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Procedures for Investigating Suspicious Outbreaks of Infectious Disease in a Noncooperative Environment

Jonathan B. Tucker, Editor

Proceedings of a workshop held in Livermore, California
May 12–13, 1998

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Monterey Institute of International Studies

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Center for Global Security Research

Lawrence Livermore National Laboratory
University of California, Livermore, California 94551

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Introduction 1

Since early 1995, an Ad Hoc Group of States Parties to the 1972 Biological and Toxin Weapons Convention (BWC)[1] has met periodically in Geneva, Switzerland, to develop procedures for a compliance protocol to strengthen the treaty, which currently lacks formal verification measures. In mid-1997, the Ad Hoc Group began to consider draft language for a protocol in the form of a "rolling text," and some delegations hope to conclude the negotiations in 1999.

The future BWC compliance regime is expected to include provisions for field investigations of suspicious outbreaks of infectious disease. Such outbreaks might be related to:

- the covert use of a biological-warfare (BW) agent against a state-party, in which case the victimized country is likely to cooperate fully with a field investigation to determine if a deliberate attack has occurred;
- the accidental release of a BW agent from a facility involved in an offensive development or production program, in which case the state-party in question is less likely to cooperate because of the consequences of being found in non-compliance with its obligations under the BWC; or
- the accidental release of a potential BW agent associated with a legitimate commercial production plant or defense-related activity, which would not constitute a violation of the BWC.

The challenge facing a future investigation team will be to distinguish between an outbreak of disease arising from natural causes or an accidental release from a legitimate facility such as a vaccine plant, and one resulting from the deliberate or accidental release of a pathogen or toxin in the context of an offensive BW program. In the latter case, the investigation would probably be complicated by non-cooperation and deception on the part of the host country.

To clarify a number of technical and political issues related to the conduct of field investigations under the future BWC compliance protocol, the Center for Nonproliferation Studies (CNS) at the Monterey Institute of International Studies and the Center for Global Security Research at Lawrence Livermore National Laboratory (LLNL) co-sponsored a workshop on May 12-13, 1998. Some 40 epidemiologists,

microbiologists, and diplomats from France, Japan, South Africa, the United Kingdom, and the United States were in attendance (see Appendix D: List of Workshop Participants).

The May 1998 workshop was the third in a series addressing technical and procedural issues related to BWC compliance monitoring. Previous workshops examined the utility of sampling and analysis for monitoring compliance, and procedures for conducting challenge and non-challenge inspections of facilities relevant to the Convention.[2]

The first morning of the *Workshop on Procedures for Investigating Suspicious Outbreaks of Infectious Disease in a Noncooperative Environment* was devoted to background briefings. Dr. James LeDuc of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, gave a presentation on domestic and international investigations of natural disease outbreaks. Harvard University Professor Matthew Meselson and Boston College Professor Jeanne Guillemin then discussed their epidemiological investigation of the 1979 outbreak of human anthrax in the Soviet city of Sverdlovsk (today Yekaterinburg), which found compelling evidence that the epidemic had been caused by the accidental release of an aerosol of anthrax spores from a Soviet military microbiological facility.

To give workshop participants a scientific introduction to plague, Dr. David T. Dennis of the CDC's Division of Vector-Borne Infectious Diseases in Ft. Collins, Colorado, presented a "primer" on the disease (see Appendix A). Then Gray Handley, the science attaché at the U.S. Embassy in New Delhi, discussed political and logistical aspects of the 1994 plague outbreak in the Indian city of Surat.

During the afternoon session, participants were organized into four working groups to discuss various aspects of a hypothetical scenario involving an unusual outbreak of pneumonic plague in a fictitious country called the Republic of Nobuti. The scenario was written by Dr. Jonathan B. Tucker of CNS with the technical assistance of Dr. Kathleen Bailey of Lawrence Livermore National Laboratory (LLNL), Dr. Stephen M. Ostroff of the CDC in Atlanta, Dr. Julie Pavlin of the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, Maryland, Dr. Donald Prosnitz of LLNL, Eileen Vergino of LLNL, and Professor Mark Wheelis of the University of California at Davis.

The four working groups focused on the following topics: (A) initiation of a field investigation; (B) conduct of a field investigation; (C) transition to a facility investigation; and (D) conduct of a facility investigation. Each working group received the background portion of the scenario and additional sections relevant to its issue-area, along with a set of discussion questions. After the working group had discussed the questions in detail, a rapporteur prepared a summary of the group's findings and conclusions. (The working group rapporteurs were Mark Wheelis, Jonathan Tucker, Kathleen Bailey, and Jason Pate.) On the second day of the workshop, the four working groups presented their reports in plenary session for general discussion.

The workshop scenario is provided in its entirety in Chapter 2. Subsequent chapters summarize the major findings and conclusions that emerged from the four working groups and the plenary sessions. All discussion was conducted on a not-for-attribution basis to encourage a free and open exchange of views.

Disclaimer

The summaries of discussion do not necessarily reflect the official views of any government nor should they imply endorsement by the workshop participants of any of the ideas and opinions expressed below.

References

1. The official name of the BWC is "Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction."

2. Published proceedings of the two previous workshops are available from the Center for Global Security Research at Lawrence Livermore National Laboratory under the following titles: Jonathan B. Tucker (ed.), *The Utility of Sampling and Analysis for Compliance Monitoring of the Biological Weapons Convention: Proceedings of a Workshop Held in Washington, D.C., October 7-8, 1996* (Livermore, CA: Lawrence Livermore National Laboratory, Report No. CGSR-97-001, February 1997); Jonathan B. Tucker (ed.), *Inspection Procedures for Compliance Monitoring of the Biological Weapons Convention: Proceedings of a Workshop held in Livermore, California, May 29-30, 1997* (Livermore, CA: Lawrence Livermore National Laboratory, Report No. CGSR-97-002, December 1997).

The Workshop Scenario 2

An Suspicious Outbreak of Plague in the Republic of Nobuti

The Republic of Nobuti is a densely populated country that is undergoing rapid industrialization and economic growth. As in many parts of the developing world, a major disparity in wealth separates a small, privileged elite from the impoverished masses. Beyond the challenges of economic development, the Nobutan government faces chronic security problems. It has been engaged for years in counterinsurgency warfare against a small but tenacious rebel group in the north of the country, and it also faces an unfriendly neighbor to the west—the Democratic Republic of Ripurna—with whom it has fought several skirmishes over a contested border. The Republic of Nobuti is an original party to the 1972 Biological and Toxin Weapons Convention and, under the Compliance Protocol, has declared two biodefense facilities that it claims are developing detectors, protective equipment, and vaccines.

Nobuti is situated in a subtropical zone and experiences heavy rains during the winter months and sweltering heat in the summer. Outside the more affluent neighborhoods of the major cities, health care and sanitation are rudimentary. On the outskirts of the cities, migrants from the impoverished countryside are crowded into vast, teeming shantytowns where there is a high incidence of various infectious diseases, including malaria, measles, and dengue fever, and occasional cases of polio.

The Nobutan city of Bisfah has a population of approximately 600,000, and the city has a concentration of heavy and light industry. Located near the geographical center of the country on flat terrain, Bisfah is a river port and a major rail hub and provides regular cargo and passenger service to the capital, Nobuti City, and other major cities. A famous tourist attraction, the Sapphire Temple, brings visitors to Bisfah from around the world.

In recent years, the Nobutan government has placed a strong emphasis on industrial development in the biotechnology and pharmaceutical sectors, including the production of vaccines against endemic diseases. To this end, the government has subsidized the construction of a biotechnology park in the Special Economic Zone (SEZ) on the outskirts of Bisfah. Lured by attractive tax concessions and a relatively skilled but low-cost workforce, subsidiaries of

several Western pharmaceutical companies have opened research and development or production facilities in the SEZ.

The Disease Outbreak

On September 21, 2001, the Doctors of Mercy, a Western missionary group working with the poor of Bisfah, learns of a serious outbreak of a fatal illness in Lanaville, a sprawling shantytown bordered on the north by the SEZ and on the south by the main railroad line and the Bisfah Train Station. Approximately 65 people, including men, women, and children, have become ill and many have already died. The illness is characterized by high fever, cough, respiratory congestion, hemorrhagic pneumonia, and shock leading to rapid death. In several cases, the disease has affected two or more members of the same family.

Most of the cases have gone to the local hospital and some to the Doctors of Mercy clinic. But neither of these facilities has much laboratory diagnostic capability, and few therapeutic options are available for treating the cases. The cause of the outbreak remains unclear to the foreign doctors, many of whom have been working in Bisfah for less than a year. New cases continue to appear in the community, although at lower numbers than during the first few days. A physician working with the missionary group sends an e-mail message about the outbreak to the Program on Monitoring Emerging Diseases (ProMED), an Internet web site that compiles epidemiological information. The purpose of the e-mail is to alert the global community to the outbreak and seek information about the possible cause.

Nobutan Government Response

Over the next few days, Nobutan public health officials arrive in Bisfah to investigate and assess the epidemic, which has generated considerable concern both within and outside the Lanaville district that appears to be the focus. Since the disease has a high fatality rate, the cause is unknown, and the potential for person-to-person transmission is unclear, the authorities impose a quarantine on the entire city of Bisfah until these issues can be clarified. Train and bus connections are cut off, and soldiers erect barricades on all major roads leading out of the city. No one—including foreign journalists—is allowed to leave or enter. As these measures are being implemented, a number of cases of a similar fatal illness are reported in other parts of Nobuti. Several of these cases involve individuals who are either residents of Bisfah or who had recently visited the city or passed through it on trains. With the recognition of cases in other parts of the country, the level of concern mounts rapidly.

A large number of messages are logged on ProMED concerning the Nobuti outbreak. Several of the messages remind readers that an outbreak of plague, including both bubonic and pneumonic forms, occurred in Nobuti seven years earlier. Areas near Bisfah were affected by the previous outbreak, which also occurred in late summer. At that time, domestic and international public-health experts ascribed the epidemic to poor sanitation coupled with flooding from unusually heavy summer rains, forcing plague-infected rats out of their normal habitat to higher ground. But investigations of the earlier outbreak were controversial. Some experts claimed that the disease was not plague and that incompetence on the part of local health authorities had led to a failure to diagnose and control the epidemic. There were also allegations that the earlier outbreak was nefarious in nature.

Over the next several days, additional cases of the fatal respiratory illness are reported in Bisfah, strongly suggesting ongoing person-to-person transmission. The quarantine of the city continues. Under the

International Health Regulations, Nobuti is required to report cases of plague to the World Health Organization (WHO) within 24 hours, yet the government plays down the reports of fatal illness and notes that the diagnosis has not been definitively confirmed.

Finally, an official with the Nobutan Ministry of Health issues a statement that a small outbreak of suspected plague has occurred in Bisfah but that there is no cause for public alarm. Because the Nobutan health authorities learned a great deal from the earlier outbreak, they can properly diagnose and treat plague cases in Bisfah and elsewhere, and international assistance is not required. The spokesperson stresses that the Nobutan government expects to have laboratory confirmation of the diagnosis in the next several days, and that the quarantine will remain in place until it is certain that the outbreak has been contained. The Nobutan Ministry of Trade, concerned over the potential loss of tourist revenue, attempts to minimize international press coverage of the outbreak.

Denial of the WHO Request

Based on the earlier outbreak of plague in Nobuti, WHO headquarters in Geneva, Switzerland, sends a formal request to the Nobutan Ministry of Health to grant access to an international team of investigators who would provide assistance in confirming the diagnosis. The WHO team would include plague specialists as well as experts in other diseases, in case the diagnosis proves erroneous. After hesitating for two days, the Nobutan government turns down the WHO request on the grounds that, thanks to the quarantine and the rapid government response, the outbreak has been brought under control.

A few days later, the Nobutan health authorities release additional information about the Bisfah outbreak. The disease has now been confirmed as plague by isolating *Yersinia pestis*, the bacterium that causes the disease, from blood specimens taken from the most recent cases. According to the Ministry of Health, the outbreak began when unusually heavy rains during the summer months led to flooding, resulting in a substantial migration of rats into the Lanaville area. The rats carried infected fleas that spread plague to the human population. Cases that appeared in other parts of the country were all related to persons who had been in Bisfah or had been in close contact with infected individuals. The Nobutan authorities indicate that the total number of cases is less than 100, although several suspected cases have not yet been confirmed. The authorities also report that the number of new cases in Bisfah and other parts of the country is dwindling.

To back up its story, the Nobutan Ministry of Health sends several blood samples and cultures, which were reportedly taken from victims of the disease in Bisfah and elsewhere in Nobuti, for analysis at the WHO Collaborating Centers on Plague in the United States and Russia. Testing of these specimens reveals the presence of a strain of *Yersinia pestis* similar to ones previously seen in the Bisfah region and susceptible to antibiotics commonly used to treat plague, such as tetracycline and streptomycin.

Failure to Control the Epidemic

Despite the quarantine of Bisfah and the reassuring statements from the Nobutan government, word trickles out over the next few days that the outbreak may not be under control. Although antibiotics were given prophylactically to large numbers of persons throughout the city, new cases of hemorrhagic pneumonia continue to be reported. Among the new cases, mortality remains high (about 85%) despite government assurances that appropriate antibiotics are being administered. Indeed, several

healthcare workers in the Bisfah General Hospital have contracted the illness and died, even though they were receiving appropriate prophylaxis.

Two weeks after the first reports of the outbreak, a Nobutan physician at the hospital posts an anonymous notice on ProMED stating that new cases of the disease are appearing daily, despite widespread antibiotic prophylaxis. The disease appears to be spreading from person to person. These observations suggest either that the diagnosis of plague is wrong or that the illness is non-responsive to antibiotics normally used to treat the disease. Panic among the local population continues to grow, and some people attempt to leave the city illegally, causing the Nobutan authorities to strengthen perimeter controls. A group of terrified residents attempting to flee Lanaville is dispersed by Nobutan troops using clubs and tear gas.

Local public-health officials in Bisfah, feeling overwhelmed by the outbreak and apparently unable to control it, petition the Nobutan government to request international assistance, but their pleas are turned down. Meanwhile, e-mail and fax communications to the outside world report that Nobutan soldiers wearing gas masks are spraying insecticides for flea control in the affected areas of Lanaville and have launched a major rodent extermination campaign. A videotape smuggled out of the country and broadcast on CNN International shows dying patients lying on makeshift cots in the corridors of a crowded hospital ward.

Based on this disturbing evidence, WHO officials repeat their request to send in an investigative team and threaten to invoke their authority under the International Health Regulations to investigate plague outbreaks. They warn the Nobutan authorities of the dire consequences of failing to control the epidemic. After two more days of political pressure from the WHO and other countries, the Nobutan government finally backs down and agrees to allow a multinational public-health team under WHO sponsorship to come to Nobuti. The Nobutan government restricts the team's access, however, to the city of Bisfah.

The WHO Investigation

The WHO investigative team, consisting of six international experts (two epidemiologists, an entomologist, a zoologist, a microbiologist, and a physician specializing in plague), arrives in Nobuti three weeks after the outbreak began. All of the team members have been vaccinated against plague. They meet in Nobuti City with Ministry of Health officials with whom they have worked cordially in the past, yet who now treat them coldly and seem determined to create bureaucratic obstacles to impede the investigation. The WHO experts suspect that the mid-level Nobutan representatives have been ordered by more senior officials not to cooperate. Because of problems in arranging for interpreters, transportation, and access permits to the quarantined city, three days elapse before the team can travel to Bisfah.

Once the WHO investigators arrive in the terror-stricken city, they find that local cultural practices complicate their work. According to religious tradition, bodies must be cremated within 24 hours of death, so that few autopsies have been performed. Microbial specimens have been poorly stored, resulting in secondary bacterial and fungal overgrowth that makes it impossible to isolate plague bacilli. Moreover, since tissue specimens have been fixed in formalin, bacterial cultures cannot be performed. Local hospital records are initially unavailable and, when released, appear incomplete.

Given these constraints, the WHO team focuses its efforts on several areas. The physician reviews the treatment of recently recognized cases and examines infection-control measures to reduce the risk to local

healthcare workers. The epidemiologists establish a case definition for the illness and investigate the circumstances of the first recognized cases in the outbreak by conducting house-to-house interviews in the Lanaville area with the assistance of local interpreters. The microbiologist concentrates on obtaining good clinical samples from hospitalized patients who meet the surveillance case definition.

Results of the Epidemiological Survey

The epidemiological investigation yields some intriguing findings:

1. Plotting of the onset dates of the early cases (epidemic curve) shows that the outbreak began explosively, with a burst of cases of hemorrhagic pneumonia.
2. Placement of the nighttime residence locations of the early plague cases on a spot map shows that they are not widely distributed throughout Bisfah but are focused in Lanaville. Even in Lanaville, the outbreak appears to have originated within a limited geographic area.
3. The initial cases all appear to be pneumonic in form—if plague is indeed the cause of the outbreak. No illnesses compatible with bubonic plague are recognized or reported during the survey, and no cases of bubonic plague were reported prior to the current outbreak.

Taken together, these findings are atypical for an outbreak of pneumonic plague. This illness usually follows an initial outbreak of bubonic plague and is characterized by person-to-person transmission through close contact, yet in Bisfah the explosive onset of a number of pneumonic illnesses is more suggestive of collective exposure. The typical epidemic curve for pneumonic plague shows a few early cases followed by a rising daily number indicative of ongoing person-to-person transmission. In Lanaville, in contrast, a large number of early cases was followed by a subsequent decline. Secondary person-to-person transmission, as manifested by additional cases within households or from other direct contact, occurred after the first few days of the outbreak (**Figure 1**).

Mapping the residences of patients whose onsets of illness were in the first 10 days of the epidemic show that 90 percent live within an area of Lanaville located south of the Special Economic Zone and north of the Central Train Station (**Figure 2**). Demographic information from early cases suggest that all ages and both sexes were equally affected (**Figure 3**). The lack of prior cases of bubonic plague and the location of the Lanaville slum are puzzling to the investigative team. Lanaville lies several kilometers from the neighborhoods along the river where the worst flooding occurred. During the survey of the affected zone, residents did not report an unusual number of rats or other rodents, and evidence for a large-scale infestation was not apparent.

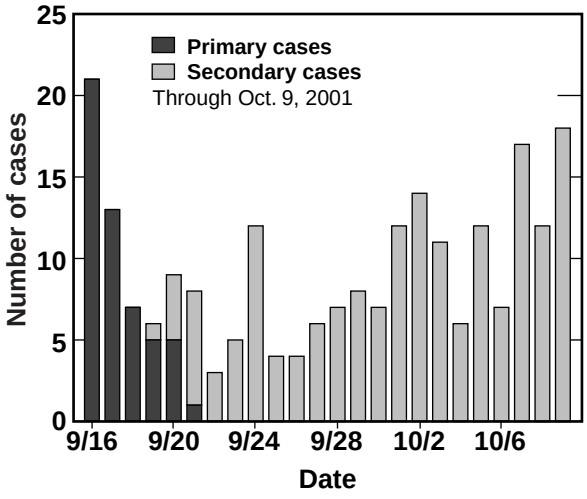

Figure 1. Pneumonic plague by onset data, Bisfah, Sept–Oct 2001.

Diagnostic tests on the specimens shipped by the Nobutan government to the Collaborating Centers are reported to the WHO investigation team as confirmed plague, yet the epidemiological evidence collected thus far is ambiguous. Also raising doubts in the investigators' minds is the poor clinical response to standard antibiotic therapy shown by patients in the hospital, and the apparent lack of efficacy of antibiotic prophylaxis, despite data from the Collaborating Centers indicating that the strains tested were sensitive to standard antibiotics.

Rodent and Flea Survey

To clarify the situation, the WHO team requests more information about the cases occurring in other Nobutan cities. The investigators also decide to proceed with studies of the local rodent population to confirm the presence of plague in the environment. Rodents are trapped in Lanaville on three consecutive nights. The trap success rate is not excessively high, suggesting that the population density of the rats

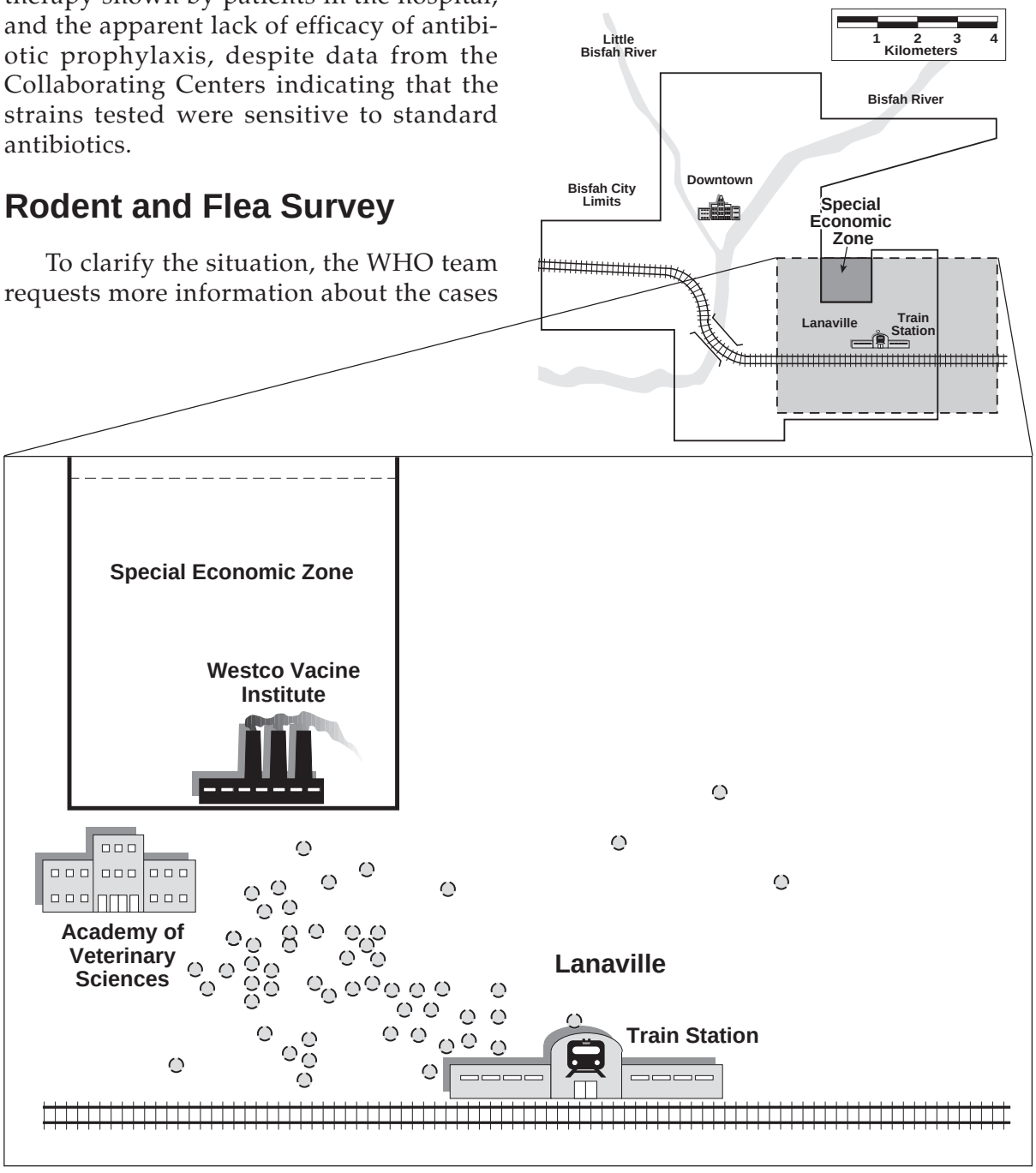

Figure 2. Plague Cases in Lanaville, Sept 16–26.

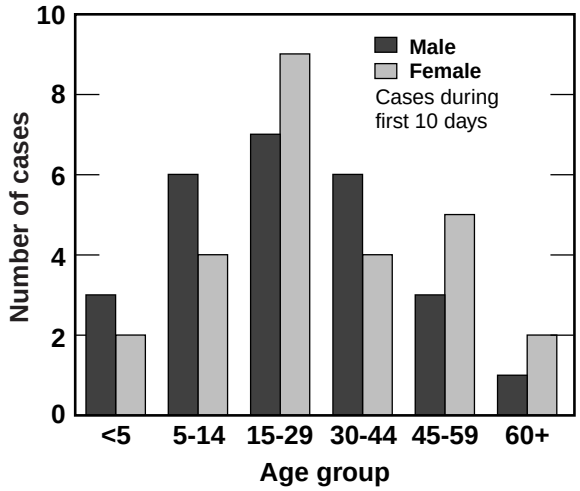

Figure 3. Pneumonic plague, Bisfah 2001, primary case age distribution.

is what would be expected in a non-epizootic situation. The WHO team also takes blood samples from the trapped rodents. Using serologic kits he has brought with him, the microbiologist finds low levels of seropositivity for plague. Fleas combed off the trapped rodents are shipped to the WHO Collaborating Centers, where they also test negative for plague.

Working in a makeshift laboratory at Bisfah General Hospital, the team's microbiologist is finally able to culture plague bacilli from blood specimens taken from recently hospitalized patients prior to their receipt of antibiotics. Although the microbiologist cannot perform advanced molecular-genetic studies on the isolates, he identifies the strain with DNA probes and performs antibiotic susceptibility testing. In contrast to the isolates sent by the Nobutan government to the WHO Collaborating Centers in the United States and Russia, the newly isolated strain has atypical growth characteristics and appears to be resistant to multiple antibiotics normally used to treat plague.

When informed of these findings, the Nobutan national health authorities respond that the indigenous strain of *Yersinia pestis* has apparently developed drug resistance during the outbreak because of the excessive and inappropriate use of antibiotics. After the WHO experts counter that drug resistance would not develop so quickly, the Nobutan authorities determine that they inadvertently shipped the wrong strain to the WHO Collaborating Centers for analysis—an honest mistake—and that the strain now being identified in Bisfah is similar to the one isolated earlier. In response to this admission, the WHO team issues an urgent request to member countries that expensive antibiotics to which the plague strain is not resistant, but that are unavailable in Nobuti, be shipped immediately to Bisfah and other affected locations.

Investigation of Cases in Other Cities

The WHO team's proposal to the Nobutan government authorities to investigate suspected and confirmed plague cases elsewhere in the country is initially rebuffed. The authorities claim that all Nobutan personnel who could assist the WHO team are working on the Bisfah outbreak and cannot spare the time to travel elsewhere. In addition, the authorities are nervous that people who have been in the quarantine zone for extended periods might inadvertently spread the disease. They also insist that the cases outside Bisfah have been thoroughly investigated and would not contribute additional useful information.

Extensive negotiations ensue. Finally, WHO team members are granted permission to visit families of early plague cases in Nobuti City and Surawantra, a large city located between Bisfah and the capital. Families of 10 early cases are interviewed. The interviews disclose that four of the 10 are residents of Bisfah who left the city on business or to visit relatives in Surawantra or Nobuti City. Five others had been visitors to Bisfah. Two of the five were visiting relatives in Lanaville, while three were conducting business in the Special Economic

Zone. One stayed in Lanaville to save money, while the other two stayed elsewhere in the city. The tenth case had been travelling to Nobuti City on the train when it made an unscheduled stop for two hours in the Bisfah Train Station for repairs. This individual had dinner at a restaurant in Lanaville and then reboarded the train.

Over the next week, emergency shipments of advanced antibiotics arrive in Nobuti and are distributed to people living in Lanaville, the area of greatest risk. This measure, coupled with intensified surveillance to identify new cases and treat them immediately with antibiotics, as well as the implementation of strict infection-control measures in hospitals, finally brings the outbreak under control. The total number of fatalities caused by the epidemic is estimated at about 500, although record-keeping is poor.

Findings of the WHO Investigation

Before leaving the country, the WHO investigative team holds a debriefing for government officials in Nobuti City. The team indicates that it has a number of concerns about the findings of its investigation, including the epidemiological features of the early cases, the low rodent population and lack of evidence of infection in the rodents, and the multidrug-resistant nature of the outbreak strain. In response to these concerns, the Nobutan health authorities reveal that they have some new information. They contend that the outbreak appears to have started when a Nobutan merchant family returned to Bisfah from East Africa apparently infected with plague. On its return, the family stayed with relatives in Lanaville, explaining the explosive onset of cases. Multidrug-resistant strains of plague have been well documented in East Africa, which would account for the lab findings. If the index cases had developed bubonic plague that had progressed to the pneumonic form by the time they returned to Lanaville, then all of the other cases were presumably infected by person-to-person contact rather than through infected rats and fleas.

The Nobutan government's hypothesis provides possible explanations for the epidemiological findings, but vague suspicions remain. After the WHO team departs Nobuti, the investigators issue a report concluding that although the plague epidemic may have resulted from natural causes, they "cannot exclude the possibility that the outbreak was a non-natural event."

Field Investigation Request

In response to the WHO findings, the Democratic Republic of Ripurna—Nobuti's hostile neighbor—files a request for a field investigation of the outbreak with the Biological Weapons Convention Organization (BWCO), the international body created to implement the new BWC Compliance Protocol. To back up its request, the Ripurnan government refers to human intelligence reports indicating that Nobuti has a clandestine biological weapons program, including the production of a strain of plague that has been selected for resistance to multiple antibiotics. Ripurna also claims that Nobuti has hired former biological weapons scientists from abroad, specialists who have employed recombinant DNA technology to enhance the aerosol stability of *Yersinia pestis* by making it more resistant to desiccation. The BWCO Executive Council, called into emergency session, considers and approves the Ripurnan government's request for a multinational field investigation in Nobuti.

Initiation of the BWCO Investigation

The BWCO Technical Secretariat assembles a multinational inspection team made up of experts on plague, biological weapons, and industrial microbiology. The team reviews the WHO team's epidemio-

logical findings and the Nobutan government's declaration of relevant facilities under the BWC Compliance Protocol. The inspectors note that the national declaration includes the Westco Vaccine Institute, a civilian pharmaceutical facility located in the Special Economic Zone that develops and produces vaccines against several endemic diseases (not including plague). The vaccine plant is a joint venture between a Nobutan limited liability company and a major Western pharmaceutical manufacturer.

The BWCO investigation team arrives in Nobuti in early November, six weeks after the start of the outbreak and just after the quarantine of Bisfah was lifted. After three days of meetings with Ministry of Health officials in Nobuti City and repeated delays to obtain permits and make logistical arrangements, the team finally receives permission to travel to Bisfah. Although the team leader has requested the right to conduct an investigation in all Nobutan cities where cases of plague have been reported, the Nobutan authorities restrict the perimeter of the investigation to Lanaville.

Upon their arrival in Bisfah, the BWCO investigators perform an epidemiological survey in Lanaville to confirm the WHO team's findings, while placing greater emphasis on ensuring the chain-of-custody of samples and carrying out forensic analytical tests. The tight clustering of cases in the section of the shantytown south of the Special Economic Zone appears to implicate the Westco Vaccine Institute, which has been declared to the BWCO as a legitimate production plant. Company executives—including representatives of the Western partner firm—insist that the facility is innocent.

On the basis of the epidemiological evidence, the investigation team requests permission from the BWCO Executive Council to conduct an inspection of the Westco facility. After extensive deliberations within the Executive Council, permission is granted. Although Westco is concerned about protecting its proprietary trade secrets, it does not oppose the inspection because it is determined to prove its innocence.

Inspection of the Westco Plant

The Westco Vaccine Institute has a standard level of security for a pharmaceutical facility, including a high chainlink fence, security guards, and controlled access. The plant's manufacturing wing contains sophisticated, dual-capable equipment for vaccine production, including glass-lined fermentors that can be steam-sterilized in a few hours without disassembly. Because the plant operates according to Good Manufacturing Practice (GMP) standards, it maintains meticulous records, all of which appear to be in order. Sampling from the production line reveals the presence of attenuated strains of typhoid fever and cholera consistent with the declared production of vaccines at the site, but not the virulent, antibiotic-resistant strain of plague that has infected nearby residents. In sum, nothing implicates the facility in the plague outbreak.

New Evidence Implicates Veterinary School

Meanwhile, an analyst on the staff of the BWCO Technical Secretariat reexamines the epidemiological data collected earlier in Lanaville by the WHO investigation team. She finds that the initial survey was misleading because it recorded the residence locations of both primary and secondary cases of pneumonic plague, which were scattered throughout the district south of the Special Industrial Zone. When she plots just the residence locations of *primary* cases reported during the first three days of the outbreak, the cases are clustered along a narrow axis oriented south-southeast of the Bisfah Academy of Veterinary Sciences, about a half-mile from the Westco facility (**Figure 4**). Meteorologi-

cal data indicate that during mid-September, the prevailing winds in Bisfah blew along precisely this axis.

The Bisfah Academy of Veterinary Sciences is owned and operated by the Nobutan Ministry of Agriculture. Based on the epidemiological data, the BWCO analyst concludes that the veterinary school may contain a clandestine biological weapons facility that was involved in production of a virulent, multidrug-resistant strain of plague. She speculates that an accidental breach of the facility's containment system on a night in mid-September caused the release of a low-concentration aerosol of plague bacteria, which was carried by a gentle breeze in a narrow plume over the densely populated area of Lanaville southeast of the veterinary school.

The timing of the accidental release can be estimated by determining when people waiting on the platform of the Bisfah Train Station were exposed to the plume. Case number 10 is a man whose train made an unscheduled two-hour stop in the Bisfah Train Station for repairs. The fact that this individual later developed pneumonic plague suggests that the exposure took place between 10:53 pm on September 14 and 1:04 am on September 15. All of the other cases are consistent with this timing. (**Table 1**).

A second BWCO analyst does a database search of scientific papers published by the veterinary school faculty and finds an unusual number of foreign experts on plague. Based on this circumstantial evidence, the BWCO investigation team re-

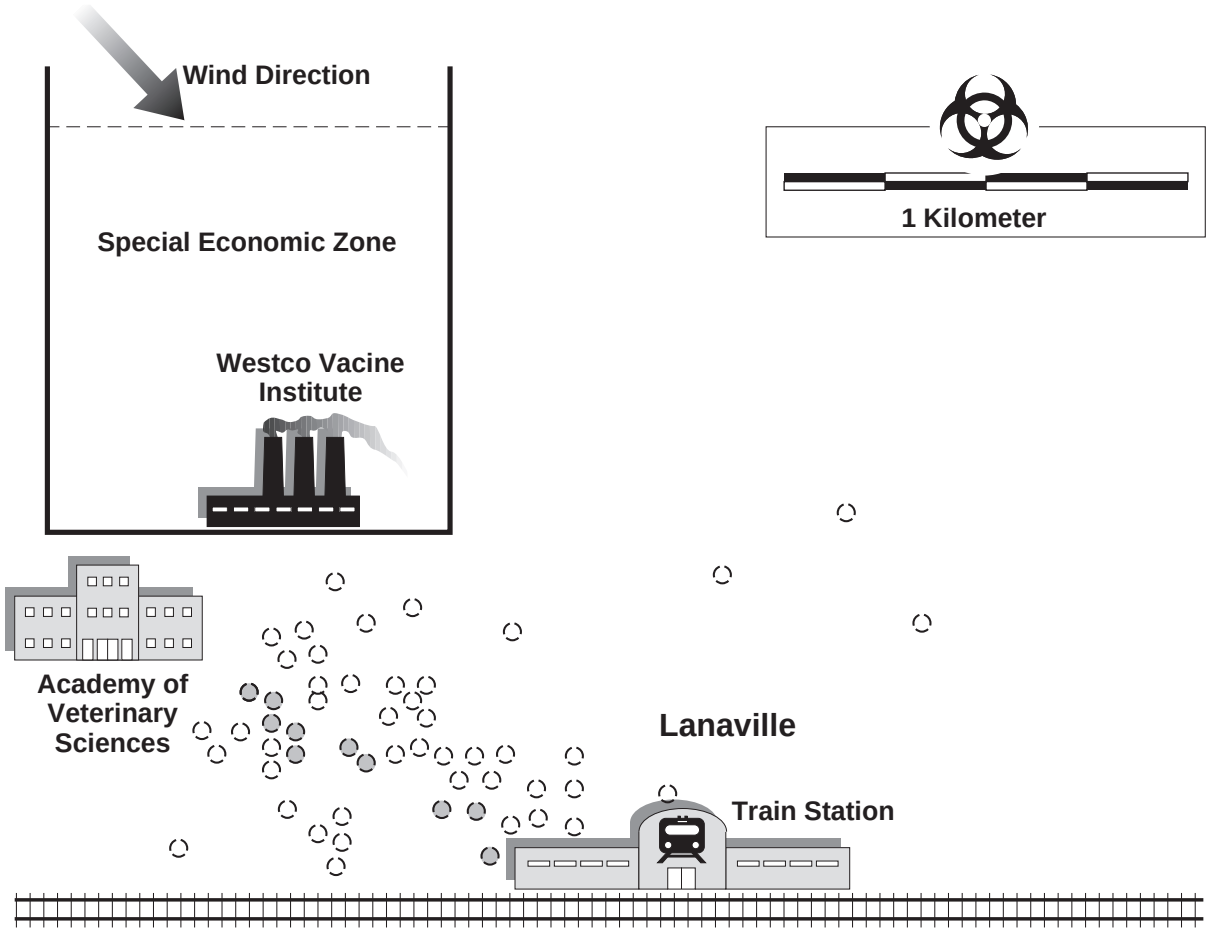

Figure 4. Primary plague cases in Lanaville, Sept 16–19 (shaded dots).

Table 1. Ten cases identified outside of Bisfah, all of whom departed by train.

Case Number	Age/Sex	Status	Dates in Bisfah	Time Departed	Onset of Illness
1.	26/female	resident	up to Sept. 14	11:05 pm	Sept. 16
2.	22/male	resident	up to Sept. 15	6:12 am	Sept. 18
3.	42/female	resident	up to Sept. 15	1:04 am	Sept. 17
4.	33/female	resident	up to Sept. 15	12:00 noon	Sept. 17
5.	18/female	visitor	Sept. 10–15	1:04 am	Sept. 16
6.	57/female	visitor	Sept. 8–15	12:00 noon	Sept. 17
7.	35/male	business	Sept. 12–15	2:14 am	Sept. 16
8.	27/male	business	Sept. 11–14	12:27 am	Sept. 16
9.	40/male	business	Sept. 13–15	1:04 am	Sept. 19
10.	35/male	traveled through on train	Sept. 14, arr. 10:53 pm	1:04 am	Sept. 17

quests and receives permission from the Executive Council to inspect the Bisfah Academy of Veterinary Sciences.

Inspection of the Veterinary School

The Bisfah Academy of Veterinary Sciences encompasses several classroom buildings, animal houses, and a research and development laboratory. The Nobutan government has not declared this laboratory under the BWC Compliance Protocol, claiming that it does not meet the declaration criteria. After the BWCO investigation team notifies the Nobutan government of its intent to visit the Academy of Veterinary Sciences, government officials restrict the perimeter of the inspection to the school grounds. In order to safeguard proprietary information, they also deny the team permission to review the laboratory records or to take samples of seed cultures stored in refrigerators on-site.

When the inspectors arrive, they determine that the research and development laboratory includes 120-liter desktop fermentors, containment hoods, freeze-driers, and a small aerosol test chamber. The presence of this equipment suggests that the facility should have been declared and hence is in violation of the BWC Compliance Protocol. Moreover, the desktop fermentors are spotless and smell strongly of bleach, suggesting a recent effort to clean up the facility.

The BWCO team is allowed to take swab samples from benchtops in the laboratory and production area, and does so in the hope of picking up identifiable DNA fragments. After on-site PCR analysis of these samples provides suggestive but ambiguous results, the samples are shipped to a BWCO reference laboratory for subtyping and comparison to a DNA sequence database. This analysis determines that two of the samples contain DNA sequences from a virulent, antibiotic-resistant strain of *Yersinia pestis* closely resembling the strain present in bacterial isolates from the Lanaville plague victims.

Epilogue

The investigators record their objective findings in their inspection report, which is

distributed to BWCO member-countries for review. Although some countries interpret the team's findings as indicating that Nobuti has violated the BWC, the Nobutan authorities insist that they have been unjustly accused. They contend that initial diagnostic testing of specimens from infected plague victims took place in the veterinary school laboratory, which would account for the traces of bacterial contamination.

A month after the inspection, the Nobutan government-controlled newspaper publishes a front-page story with the banner headline, "Nobutans are Guinea Pigs in Germ War Test." The article alleges that the U.S. military has covertly released a genetically engineered strain of plague in Bisfah as a means of testing a new generation of deadly biological warfare agents. U.S. government officials reject these allegations as absurd, but several countries hostile to Washington find them credible. The BWCO Conference of States Parties, called into special session to address the controversy, is unable to reach consensus on whether or not Nobuti has violated the BWC.

Initiation of a Field Investigation 3

Workshop participants generally found the outbreak scenario to be realistic. They also agreed that the epidemiological evidence included in the scenario provides a strong *prima facie* case that the plague outbreak in Nobuti may be of nonnatural etiology, warranting a decision to investigate the situation by the Biological Weapons Convention Organization (BWCO), the international organization that is likely to be established to implement the future BWC compliance protocol.

The evidence supporting the investigation request includes an explosive epidemic curve indicative of the simultaneous aerosol exposure of a large number of people, a tight geographic clustering of cases, and the first known outbreak of pneumonic plague in Nobuti involving a multiple-antibiotic-resistant strain. While this evidence does not in itself prove an unnatural cause, it is strongly suggestive and should easily warrant a field investigation. Even so, it is remotely possible that the outbreak is of natural origin, particularly if the identification of cases by the WHO team is incomplete. For this reason, independent supporting evidence provided by states-parties would strengthen the case for a BWCO investigation.

Some participants noted that in an actual investigation, the WHO team would have uncovered certain types of evidence that only emerge later in the workshop scenario. Such items include the detailed molecular typing of the etiologic agent, mapping of the geographical locations (both residence and work) of the primary and secondary cases, and detailed meteorological data as a logical follow-up to the possibility of aerosol exposure.

Approval Mechanism in the Executive Council

Workshop participants agreed that prior to conveying a request for a field investigation to the BWCO Executive Council (the deliberative body of member-states that oversees day-to-day operation of the organization), the director-general should consult with the accusing state-party to clarify the allegation, and with the accused state-party to clarify its defense. In addition, the BWCO Technical Secretariat should provide a technical analysis of the evidence presented by both sides to assist members of the Executive Council in evaluating the strength of the case. While it would be desirable to have a standard set of criteria that the

evidence must satisfy to warrant a field investigation, real-life epidemiological investigations are so varied and dependent on the situation that each case must be evaluated on its own merits.

The voting process in the Executive Council on field investigation requests should be structured so that frivolous or nuisance requests are rarely approved, while legitimate, substantive requests almost always are. Past precedents include the "red-light" filter specified in the Chemical Weapons Convention (requiring a three-quarters majority vote of the Executive Council to *block* a challenge inspection) and the "green-light" filter in the Comprehensive Test Ban Treaty (requiring a 60 percent majority vote of the Executive Council to *approve* a challenge inspection). As a reasonable compromise position, most workshop participants favored a "green-light" filter in which a field investigation would require the approval of 50 percent of the members of the Executive Council that were present and voting, with abstentions not counted as votes.

Availability of Intelligence Information

Particularly useful for the BWCO investigation would be reliable intelligence that lends credence to Ripurna's allegation that Nobuti has a covert offensive BW program. While it may be difficult to balance the utility of intelligence information against the need to protect sensitive sources and methods, each possessor of relevant intelligence will have to decide for itself if the advantages of releasing the information outweigh the disadvantages.

Workshop participants agreed that intelligence-sharing could play an important role in assessing requests for field investigations, but they were unable to agree on a mechanism for that purpose. Some participants argued that when the country requesting a field investigation presents its case to the Executive Council during the initial round of inquiry and decision-making, the council should have at its disposal any information that member-states decide to make available. Provision of intelligence information should not be mandatory and would be entirely at the discretion of member-states. Once such intelligence has been released, however, it would become part of the request for a facility investigation and could be used by the BWCO investigation team.

Some participants stressed that it would be inappropriate for the BWCO or the investigation team to be given access to confidential intelligence data *after* the Executive Council has approved a field investigation. In other words, the use of intelligence information would be acceptable if the providing country is willing to share it with the council during its deliberations. After a field investigation has been approved, however, it would be politically unwise for the BWCO investigation team to make use of confidential intelligence that has not been "filtered" by states-parties. The BWCO must scrupulously avoid creating any questions about its political neutrality, such as the suspicion that a member of an investigation team or anyone associated with the team is under the control of the intelligence service of a member-state. Another problem with allowing states-parties to pass confidential intelligence information directly to the field investigators is that they would not be in a good position to assess the accuracy of the information.

Some participants argued that many member-states would be unwilling to share particularly sensitive intelligence with the Executive Council but might be prepared to provide a private briefing for the BWCO director-general—and possibly the investigation team leader—about suspect facilities or the names of scientists the team should make a point of interviewing. Such information would make it possible for the team to conduct a more focused investigation. If

this information were channeled through the director-general, he or she could then decide whether or not it should be passed along to the investigation team without revealing the source.

Other participants said that it would be preferable not to formalize structures for intelligence-sharing. Any ambassador of a member-state has the right to make a private appointment with the BWCO director-general to share information informally. It was noted, however, that the Executive Council would probably object to the director-general taking the lead on intelligence-sharing, on the grounds that such information should be assessed by a larger political body.

The epidemiologists present stressed that governments should be sensitive to the limited experience of the public-health community with intelligence information and the community's need to preserve political neutrality in order to remain effective. Thus, procedures should be developed to insulate public-health workers from being tainted by an association with intelligence data.

Role of the World Health Organization

Participants agreed that the BWCO investigation team should make use of data collected by WHO, if available, but stressed that WHO's political neutrality should be protected. Being linked too closely to the BWCO would limit WHO's future ability to conduct public-health investigations.

The desirability of keeping WHO out of the BWCO's orbit raised the question of whether the two organizations should hire the same experts. In fact, a strict separation may not be feasible, given the limited number of experts around the world specializing in the epidemiology of plague and other exotic infectious diseases. The presentation by James LeDuc of the U.S. Centers for Disease Control and Prevention (CDC) made clear that countries have long neglected to train field epidemiologists capable of investigating unusual outbreaks of disease. Although steps have been taken recently to address this shortage of expertise, they are only just beginning. For this reason, it is clear that the BWCO will need to hire, presumably on a part-time basis, many of the same experts who work for WHO. Disqualifying such individuals would cripple the new organization's ability to competently investigate suspicious outbreaks of disease.

Nevertheless, a few epidemiologists and experts on infectious disease who are affiliated with WHO said they might be reluctant to serve on BWCO teams if it involved the risk of jeopardizing their political neutrality. As one epidemiologist observed, "There will probably be elements of confrontation in BWCO investigations, and very few of us are interested in being in those situations. Getting involved in something like that could potentially compromise my activities as a consultant for CDC and WHO. But it depends on the circumstances." Participants also noted that most field epidemiologists are government employees who will need official permission from their countries to serve on BWCO investigation teams. Thus, in the real world, it may be difficult to assemble field investigation teams with the requisite types of expertise.

Availability of WHO Data

Another contentious issue was whether the report of a WHO public-health investigation team should be made available to the BWCO in the context of a BWC compliance investigation. At present, the release of a WHO report requires the consent of the country that invited the team in. Workshop participants stressed the need to preserve the political neutrality and credibility of the WHO and other UN-affiliated public-health agencies, such as the International Organization of Epizootics (OIE) and the Food and Agriculture Organization (FAO), and wor-

ried that sharing of epidemiological data with the BWCO could have negative political ramifications. For example, if WHO were to make known before it began an outbreak investigation that its report could be used as the basis for a future BWCO inquiry, some countries might simply cease to cooperate with the WHO, compromising the agency's ability to perform its mission.

Avoiding the politicization of the international public-health agencies would favor a policy of continuing to require host-country approval before WHO, FAO, or OIE investigation reports are released. In the workshop scenario, however, it is unlikely that the Nobutan government would have authorized the release of the WHO report, even assuming that it was available at the time the Ripurnan government requested a field investigation. Yet without the information obtained by the WHO team, there would have been little basis for the BWCO investigation.

Workshop participants did not see an easy way out of this dilemma but discussed a number of options. First, it was noted that WHO typically releases a fair amount of epidemiological information to the public in the course of an outbreak investigation, including a series of press releases. Although the host government has a say in what types of information are released, it must contend with pressure from the media. Relevant data may also become available from other sources, such as humanitarian agencies working in the affected country or unauthorized postings on Internet sites, such as the Program on Monitoring Emerging Diseases (ProMED).

Moreover, even if the host country does not approve public release of the WHO report, it may be impossible to keep the findings completely under wraps. Since a large number of people are typically involved in an outbreak investigation and drafts are circulated for review, the information becomes relatively widely known. During the outbreak of avian flu in Hong Kong, for example, the Chinese government took four days to clear a single WHO press release, but the information was readily available from other sources. It might therefore be possible to make the case for a BWCO investigation on the basis of indirect evidence, without embroiling the WHO in a politically sensitive dispute.

In fact, WHO has moved voluntarily in recent months to adopt a higher profile on matters of international security. The agency is revising its landmark 1970 report on the health effects of chemical and biological weapons. In addition, a planning document prepared for the 1998 World Health Assembly, *Health for All in the Twenty-First Century*, makes two references to weapon issues and security matters, suggesting that WHO intends to play a larger role in this arena.[1] Paragraph 60 of the report states: "WHO aims to demonstrate that health can be a powerful bridge to peace, and will document the public health impact of weapons as a basis for preventative action." Paragraph 107 states: "International and foreign policy must be broader-based, with greater emphasis on international health security and its contribution to sustainable peace."

Even if WHO, OIE, and FAO decline to release sensitive epidemiological data to the public, some workshop participants suggested that these agencies might be willing to share such information with the BWCO director-general on a confidential basis. The director-general might in turn have the authority to brief this information—also on a confidential basis—to the BWCO Executive Council as it deliberates on a field investigation request. Such information-sharing would help the Executive Council to determine whether the statements of the accusing and accused states-parties are consistent with the available epidemiological evidence. Giving the field investigation team access to the WHO data through the BWCO director-general would help them to replicate and confirm the earlier results and

guide them to important contacts. If the WHO findings have not been approved for public release, the BWCO investigation report would not mention them.

Another possible solution would be to make the screening process for a BWCO outbreak investigation sufficiently stringent that countries would not be able to make a frivolous accusation based on a WHO report. The drawback of this approach is that it would be more difficult to get a field investigation approved when it is really warranted.

Mandate for a Field Investigation

Workshop participants agreed that the mandate of the field investigation team should be flexible and not limited to the specific allegation made by the accusing party. For example, the investigation mandate might charge the BWCO team with determining whether a disease outbreak is natural or not, and if it appears non-natural, to discover its origin. Given the mobility of cases of infectious disease and those with whom they come in contact, it would not normally be appropriate to specify a geographic perimeter for a field investigation. If such a perimeter is established, however, it should be large enough to include all known or suspected cases and their contacts. Provisions should exist to enlarge the perimeter if additional cases are reported outside the area.

The investigation mandate should authorize the team to interview all confirmed and suspected cases of the epidemic disease, their contacts, professionals involved in the diagnosis and treatment of cases, and government officials making public-health policy with regard to the outbreak. The team should also have guaranteed access to relevant hospital records, necropsy reports, laboratory test results, retained biomedical samples, and relevant background information and archival samples (e.g., from previous outbreaks of the same disease), even if these materials are stored inside industrial or military facilities, prisons, and other secure buildings. The host country should supply the team with accurate street and terrain maps. Because a satellite image cannot easily be correlated with a street address, it is useful to have a map overlay.

Finally, the investigation mandate should specify the team's right to take biomedical and environmental samples for on-site analysis, and provide for more sophisticated analysis at certified reference laboratories outside the country if the team determines they are necessary. Exported samples should be split, with a portion remaining in the custody of the host country, and strict chain-of-custody procedures employed. The host country should also have the right to have an observer accompany the sample and witness the laboratory analysis.

Participants differed, however, over the appropriate scope of the investigation. Some argued that a field investigation should be in "challenge mode" from the outset and cover all relevant facilities. Thus, if the epidemiological evidence led to a particular facility, such as the vaccine plant in the workshop scenario, the team should be empowered to inspect the facility without pausing to obtain permission from the BWCO Executive Council. Other participants countered that a field investigation should cover only those buildings containing patients, such as hospitals and clinics, and that the on-site inspection of a government or industrial site should be authorized only after compelling evidence was found to implicate it in the outbreak. Under the latter approach, the field investigation would extend up to the fenceline of a suspect facility. If the field investigation found "probable cause" of the facility's involvement in the outbreak, the team would then request a transition to a facility inspection, necessitating formal approval by the BWCO Executive Council.

One participant strongly objected to restricting the scope of a field investigation in this way, noting that the job of a field epidemiologist is to ask lots of questions and to explore every possible hypothesis for the cause of a disease outbreak. If an investigator becomes aware of a facility near the area affected by the outbreak that is a potential source of infection, it would be only natural to inspect the facility as part of a field investigation. Other participants countered, however, that giving the BWCO field investigation team *carte blanche* to inspect all potentially relevant facilities was not politically realistic.

Timeline of a Field Investigation

While it is important to get a field investigation team to the site of an unusual outbreak as soon as possible, the notification period should be on a time-scale of days, not hours. It would be a mistake to rush the Executive Council's consideration of the evidence—likely to be considerably more complex than that needed to justify a field investigation under the Chemical Weapons Convention—to meet an arbitrary and unrealistic deadline. If the BWCO team is not ready to leave immediately after the investigation is approved, a smaller advance team should be dispatched while the full investigation team is being assembled and equipped. This advance team, composed entirely or mainly of BWCO permanent staff but advised by appropriate experts, would collect time-sensitive evidence, establish communication links, organize in-country transportation, and secure relevant records.

Most workshop participants believed that a field investigation should last 30 days, with the possibility of negotiating extensions as required. Some participants, however, were reluctant to put any time limit on a field investigation and argued that the team should remain in-country for as long as is needed to identify the source of the outbreak. The political reality, however, is that it is unlikely that a BWCO investigation team would have 30 days to compete its work, and it might receive considerably less. Overcoming logistical roadblocks put up by the host country, such as problems with arranging transportation or in getting access to the affected population, will also take time to overcome.

In any event, the investigation team should focus on answering the most critical questions related to each of the competing hypotheses for the cause of the outbreak. The speed with which a field investigation can be conducted is roughly proportional to the size of the investigation team, since a large team can break up into subgroups that pursue multiple lines of inquiry simultaneously.

A related issue is whether the allotted period for the investigation should include the time required to obtain the results of laboratory analyses, particularly if samples are removed from the country for testing, or whether a time-extension will be provided for this purpose. Ideally, it would be desirable to carry out all scientific analyses while the team is still in-country so they can learn the results and then conduct follow-up investigations if necessary prior to their departure.

Composition of the Field Investigation Team

The field investigation team should be headed by a member of the permanent BWCO inspectorate staff who has been trained to conduct field investigations in a hostile political environment. Other members would be drawn from the BWCO inspectorate, the Organization for the Prohibition of Chemical Weapons (e.g., toxin experts), and a "pre-approved" list of outside experts. Such individuals would need to be fully vetted to ensure their quality, integrity, and objectivity, since countries

typically insist on screening international inspectors to remove those believed to pose a security risk. No nationals of the accused or accusing party should be allowed to serve on the investigation team, although the accusing party might be given the right to send an observer to witness—but not actively participate in—the investigation process. The host government, for its part, should have the right to provide escorts to accompany the investigators and manage access to sensitive facilities.

Participants agreed that the BWCO inspectorate should consist of a small permanent core staff of full-time inspectors, augmented with on-call experts and linguists who have been fully vetted in advance. All personnel who participate in field investigations should be selected from the "pre-approved" list to avoid an undue delay between the approval of an investigation and the arrival of the team in-country. A given BWCO investigation team might number eight to 12 people, although it could be larger for high-profile cases or smaller for minor outbreaks.

The composition of a BWCO team will vary according to the nature of the outbreak, but in general the team should include a mix of public-health and arms-control specialists, who tend to have different outlooks and methodologies. Whereas the public-health paradigm is cooperative and involves working closely with the host government to identify the source of an outbreak, the arms-control paradigm is forensic, adversarial, and more akin to domestic law enforcement in seeking to determine whether the cause of an outbreak is related to BWC noncompliance. A typical team would include a team leader, a logistics expert, an epidemiologist, an entomologist, a zoologist or veterinarian, one or more microbiologists, two skilled interviewers trained in epidemiological and medical matters, two interpreters, and a translator. In cases where a facility is implicated, experts in industrial microbiology would be valuable. At least one team member should be certified in handling and control of hazardous biomedical and environmental samples. Such requirements would make the team larger, unless it is possible to fly in additional experts to help with a facility investigation at a later stage. Members of BWCO investigation teams should also be vaccinated against as many putative BW agents as is feasible.

The team leader should be responsible for handling negotiations with the host government and for making comments to the media (which should be kept to a minimum), so that the team speaks with one voice. The experience of the UN Special Commission (UNSCOM) in Iraq suggests that team leaders require a rare combination of technical knowledge and diplomatic skills. If the host country tries to obstruct the team's investigation, the leader must be able to devise alternative tactics and circumvent obstacles in a firm and persistent manner, without becoming emotional or confrontational.

An epidemiologist from the CDC noted that when the agency conducts outbreak investigations, the team composition is not static. One reason for the turnover is that experts often cannot stay for the full 30 days. In addition, experts shuttle in and out as circumstances change and the team uncovers new leads requiring special expertise. During the investigation of the avian flu outbreak in Hong Kong, for example, the CDC team conducted interviews and collected specimens from a large number of people, many of whom had similar Chinese names. To handle this huge amount of confusing information, the team brought in a full-time staff member to enter data into a computer. Although the need for a data-entry clerk had not been anticipated at the outset, this individual soon became essential.

Accordingly, it would not be desirable to require the BWCO to specify in advance the composition of the team for the entire investigation. Instead, the inspectorate

should have the capability to deploy new members of the team—selected from the pre-approved list of experts—as the need for special skills arises. Hiring additional experts for the team from the pre-approved list should not require a decision by the Executive Council, but at most the blessing of the BWCO director-general. If the team sought to bring in an expert whose name was not on the pre-approved list, however, even the Executive Council would probably not have the authority to approve this individual over the objections of the host country.

References

1. World Health Organization, *Health for All in the Twenty-First Century*, Document No. A51/5, 1998.

Conduct of a Field Investigation 4

Workshop participants doubted there would be many requests for field investigations of unusual outbreaks of disease. As bioterrorism becomes an issue of greater concern, accusations that disease outbreaks are the result of covert BW attacks will probably become more common. Even so, most states will probably be self-deterred from requesting field investigations because they fear retaliatory requests. For this reason, only a few high-profile outbreaks per year will probably trigger a field investigation. The regime should be sufficiently flexible, however, to provide for different levels of response depending on the size and importance of an outbreak.

Approach to a Field Investigation

Since the BWCO investigation team's access to WHO epidemiological information is unclear, the BWCO team may have to replicate some or all of the WHO investigation. In any event, the BWCO investigators will have a somewhat different focus: they will need to undertake more forensically oriented activities than the WHO team and will place greater emphasis on the potential for nefarious activity. For example, the BWCO team will want to map the locations of the outbreak victims in relation to certain buildings and facilities, an action that might not be necessary for a public-health investigation. If the epidemic has ended by the time the BWCO team arrives in-country, the investigators will focus primarily on immunological techniques, such as testing blood samples from survivors for antibodies to the disease agent. Finally, the BWCO team will require a high standard of proof to demonstrate noncompliance, including stringent procedures for collecting forensic samples and ensuring proper chain-of-custody for evidence.

Workshop participants agreed that the BWCO investigation team should identify the most likely scenarios that could have caused the outbreak and seek empirical evidence to test them. Possible hypotheses to explain the workshop scenario include: (1) the official explanation of the Nobutan government that a traveler from East Africa was the index case; (2) the Ripurnan allegation that the source of the outbreak was an accidental release of weaponized plague from a Nobutan biological-warfare facility; and (3) other natural sources of the disease. At the outset of a field investigation, the

BWCO team should not take an adversarial approach but should seek to engage the cooperation of the host government in demonstrating that the allegations of a BWC violation are false. Maintaining a cordial relationship with host-country officials may necessitate some restraint with respect to the level of intrusiveness. The team should also identify sympathetic individuals in the host country with whom it can work, such as physicians concerned about the outbreak, since such professional alliances could greatly facilitate the investigation.

Lines of Inquiry

Because the BWCO team will need to pursue numerous lines of inquiry simultaneously within a limited time period—particularly if there are several competing hypotheses for the cause of the outbreak—it would be desirable for the team to break up into subgroups that work in parallel. If the BWCO team has access to WHO epidemiological data, it should evaluate that information and identify information gaps that need to be addressed.

In the workshop scenario, the WHO investigation ruled out a natural reservoir of plague in Nobuti and noted the explosive onset of pneumonic disease and the presence of an unusual, multidrug-resistant strain of *Yersinia pestis*. In conducting its own inquiry, the BWCO team might focus initially either on the peak of the epidemic curve (the bulk of the diseased population) or the outliers (such as individuals living in other cities who became ill after passing through Bisfah on trains).

During its investigation, the BWCO team will require access to medical records, mainly of victims, but also of some controls. To protect privacy, patient names should not be included in the investigation report, but the names should be recorded in a confidential file to permit follow-up. (It was noted that privacy laws differ from country to country, and that medical records may be more accessible after death.) The team should also have access to archived biomedical samples that were collected during previous disease outbreaks in the affected country. For example, the workshop scenario mentions a previous outbreak of plague in Nobuti several years earlier; it would be valuable for the BWCO team to have access to records from that outbreak and to any preserved specimens.

With respect to the epidemiological survey in the workshop scenario, it was noted that systematic house-to-house interviews of families affected by the plague outbreak would require personnel in addition to the six WHO experts, only two of whom have survey or interview experience and none of whom may have the needed language skills. In other words, if the data were not provided by local officials, the WHO investigation as described in the scenario could not have generated the epidemiological data cited. Points to consider include the number and qualifications of personnel needed to conduct the appropriate survey, the authority needed to interrogate citizens, the time required to conduct the survey and analyze the results, and the nature of the questions asked (especially as to daytime versus nighttime location of affected persons and as to the date of onset). The basic point is that the conduct of a useful survey will probably require personnel, authority, and time considerably exceeding what the described WHO team could manage. If, however, the survey data were collected by local health officials and provided to the team, it would be necessary to assess the reliability of the information.

Another issue is how the investigation team should interact with the host government's public-health activities. In the workshop scenario, the Nobutan government conducts a rodent extermination campaign. While this activity could be a legitimate effort to fight the plague epidemic, it might also be an attempt to destroy evidence of a non-natural etiology. For this

reason, the investigation team should closely monitor the actions of the host government.

Workshop participants agreed that the BWCO investigation team should give highest priority to determining if the outbreak victims lived or worked in locations along a straight line, which would provide a clear indication of exposure to a windborne BW aerosol. Since wind direction typically does not shift dramatically over a 30-minute interval, a breeze of 10 miles per hour could transport a plume of biological agent over a distance of five miles. For example, the epidemiological investigation of the 1979 anthrax outbreak in Sverdlovsk by Professor Meselson and his colleagues determined that most of the victims lived or worked along a narrow footprint four kilometers in length that extended from a military microbiological facility within the city to the southern city limit. When the researchers compared maps of the victims' daytime and nighttime locations, they noted that many of the scattered points in the former plot collapsed into a narrow zone in the latter plot. This statistically significant pattern could not have resulted from the person-to-person transmission of disease and strongly suggested that the victims had been exposed to a windborne aerosol of anthrax spores.[1]

A workshop participant noted that approximate information about daytime and nighttime population distribution is important because, in principle, it is the case *rate*, not the raw number of cases, that one wants to plot on the map. Using raw numbers rather than rates can give misleading results because cases may be concentrated in large factories or apartment houses simply because of the large number of people working or living there. To determine case rates, one needs at least rough data on population density, i.e., the locations of large factories and apartment buildings and the approximate residential population density distribution, which can be estimated from satellite photographs.

In the workshop scenario, the initial epidemiological map of the outbreak in Bisfah includes both primary cases of pneumonic plague and secondary cases caused by person-to-person transmission.[2] As a result, no clear directional indication of the source of a release is apparent: the cases are concentrated in the Lanaville shantytown but are relatively scattered. Two hypotheses are consistent with the preliminary data. First, it is possible that the victims all knew one another and were exposed when they went together to the train station to greet a plague-infected family that had just returned from East Africa. Second, it is possible that a plume of aerosolized plague was released from the Westco vaccine plant, exposing the inhabitants of Lanaville. In fact, both of these hypotheses turn out to be incorrect.

It was also noted that implicit in the workshop scenario is an interesting turn that the field investigation might take. Since the Nobutan government claims that the strain of plague responsible for the outbreak was imported from East Africa, the BWCO team might decide to expand the investigation to the country in question. Yet if that country is not a state-party to the BWC Protocol, would it grant the team access? Another unsettling possibility is that the Nobutan government, having decided to pursue an antibiotic-resistant strain of plague as a biological weapon, obtained natural isolates from East Africa by mail or by sending a microbiologist there to collect them. Thus, even if the epidemiological investigation and molecular characterization were to confirm that the outbreak strain was closely related to a natural isolate from East Africa, that finding would not necessarily clear the Nobutan government.

Interpreters and Logistics

To the extent possible, the BWCO investigation team should make its own logistical arrangements to minimize opportunities for obstruction by the host

country. Although the inspected state-party should be obligated under the BWC Protocol to provide lodging, food, and transportation for the inspectors, the host government may attempt to impede the inspection process.

The same applies to interpretation and translation services. The BWCO investigation team should assess the competence and political independence of the interpreters provided by the host government but should not rely on them exclusively. Instead, the team should bring with it at least two interpreters and a translator, particularly in a country where most people do not speak English. Interpreters should be familiar with current idioms and relevant technical terms.

A participant argued that of the BWCO team of eight to 12 investigators, two or three should be linguists. If, however, the team breaks up into subgroups conducting parallel operations, interpretation services could create a bottleneck. The team might therefore need enough professional interpreters so that one could work with each subgroup. It is not realistic, of course, to expect the BWCO to employ linguists trained in all of the world's languages. Instead, the organization should compile an on-call list of interpreters and translators who can work in the official languages of member-countries and have undergone a rigorous vetting process, much as with the list of outside scientific experts.

Conduct of Interviews

An epidemiological field investigation should include interviews with local and foreign physicians, outbreak survivors and their families, government officials involved in public-health measures such as the rat extermination campaign, facility workers and managers, and others. The BWCO team should ask for the names and addresses of all outbreak victims and request permission to interview their families. To preserve privacy, victims' names should not be linked to medical records in any public report, but a mechanism must exist for tracking the families and conducting follow-on interviews if necessary. In the workshop scenario, the BWCO team might also ask to interview workers at the Bisfah train station, the political leaders of the Lanaville shantytown, and traditional healers who could have useful information about the outbreak.

As the investigation progresses, survey researchers may need to interview the same sources repeatedly. For this reason, it is essential that the investigation guidelines permit multiple interviews. Given the limited time and resources available, however, it will be necessary to take a "triage" approach by identifying those individuals who have the most valuable information. The investigation team should also use structured interviewing techniques (e.g., questionnaires) to accelerate the process and to obtain consistent and directly comparable results.

Interviews have proven extremely valuable for UNSCOM investigations of Iraq's weapons programs, although nearly all have been conducted in the presence of a host-country official. Even if a government representative is sitting at one end of the room and the interview is conducted at the other end, the fact that the individual's identity has been compromised obviously exerts a chilling effect on the willingness of the interviewee to speak freely. Most delegations in the Ad Hoc Group are keen to protect the rights of the inspected state-party, making it unlikely that BWCO teams would be granted the right to conduct interviews without a host-state representative present. Nevertheless, there may be other ways of addressing these concerns. For example, interviews could be audiotaped or videotaped so that if the testimony is later challenged, an impartial representative could review the tapes and assess the evidence without revealing the interviewee's identity.

Workshop participants discussed whether a hypothetical field investigation of the 1979 anthrax outbreak in Sverdlovsk could have uncovered useful information through the conduct of interviews. An experienced participant noted that the difficulty of interviewing depends on where the individual sits in the political hierarchy. When talking to ordinary citizens, survey researchers often have considerable latitude to ask questions. Since the information held by disease victims or their families is not usually considered valuable by senior officials, it is relatively accessible. As one moves up the administrative hierarchy, however, interviews become more difficult and are typically observed by other officials from the host government.

Sampling and Analysis

In the workshop scenario, environmental sampling is unlikely to provide much information, particularly if the BWCO team arrives after the epidemic is essentially over. Environmental samples generally contain only minute amounts of plague bacilli, which are easily overgrown by other bacteria. One possible exception is a filtration system that extracts and concentrates plague bacilli from the air in the event of an airborne release, such as an air-conditioning filter in the Bisfah train station. In that case, microbiologists might sample the filter and use a selective growth medium to culture the plague bacilli.

Biomedical samples, in contrast, are likely to play a vital role in a field investigation. Analyzing a sample of an isolated agent can identify the microbial strain and profile its antibiotic susceptibility. In the context of the workshop scenario, comparing plague isolates from the Bisfah outbreak to an antibiotic-resistant strain from East Africa would be a good test of the Nobutan government's hypothesis that the disease originated with a recently returned traveler. Antibiotic-resistance plasmids may also contain distinctive DNA sequences suggestive of genetic engineering and possibly weaponization, although such genetic modifications may also be associated with legitimate research or natural causes.[3] For example, since antibiotic-resistance plasmids can migrate between different strains of bacteria, they may appear in a bacterial genome even if they have not been inserted deliberately. Such a scenario is in fact likely when the plasmids provide antibiotic resistance and antibiotics are present in the environment.

If the epidemic has subsided by the time the BWCO team arrives, the investigators may not have access to clinical samples from sick patients and may be limited to doing serological work on survivors.

To avoid a confrontation with the host government, sampling rights should be negotiated in advance. In general, the assumption should be that biomedical samples (blood, urine, sputum, bubo aspirates, tissue specimens from autopsies, etc.) may be collected and, if necessary, removed from the country for analysis. Team members should employ appropriate containment and shipping procedures to avoid biohazards to the team and others during the shipping process. In addition, to meet the strict evidentiary standards of a forensic investigation, the sampling process should ensure that the samples are demonstrably free of contamination and tampering by the host government. Finally, the BWCO team should ensure effective chain-of-custody for samples sent to outside laboratories for analysis.

The ability to analyze samples will hinge on the availability of good laboratory facilities in countries around the world, yet qualified diagnostic labs capable of detecting exotic infectious diseases and putative BW agents are in short supply. Indeed, key questions that should be addressed in planning for the BWC protocol are the laboratory support base for the BWCO and the need to expand the global capacity for diagnostic

testing. Where will the necessary lab work for BWC compliance monitoring be performed, by whom, and who will pay for it? Sophisticated genetic analysis is even more demanding. In general, genetic subtyping of strains will not be possible in-country but will have to be carried out in highly specialized reference laboratories, of which there are only a few in the world.

Dealing With Obstruction by the Host Country

In order to address obstruction and red tape on the part of the host country, the investigation team should maintain political pressure by remaining in continuous communication with BWCO headquarters and reporting whenever the host country denies access or otherwise seeks to block the investigation. The team also can report obstructionist activities in its final report.

Nevertheless, a country that is secretly violating the BWC is already taking a serious risk and will probably do whatever it takes to prevent the investigators from uncovering its illicit program. Indeed, obstructing a BWCO investigation is less likely to result in serious sanctions than actual proof of a BWC violation. For this reason, proliferators will probably deny access to the investigation team and take their chances with the international body.

One participant suggested that the inspectors could deter obstructionism by threatening to document such behavior in their final report. Others countered that given how seldom field investigations will take place and the political baggage that will accompany them, it is doubtful that determined proliferators would be deterred from blocking an inspection by the prospect of a negative report. The example of Iraq has unfortunately demonstrated that obstructionism works. As long as the investigation team remains in-country, however, the possibility remains that the host country will make a mistake that inadvertently reveals the existence of an illicit program.

It was also noted that the BWC Compliance Protocol will include a binding requirement for cooperation with field investigations (although this obligation will be muddied somewhat by the concept of managed access). Thus, while host-country obstructionism may prevent the investigation team from obtaining clear evidence of a BWC violation, if the obstructionism is so blatant and egregious as to represent a clear violation of the obligation to cooperate, states-parties will be able to impose sanctions on the host country for violating the Protocol. While the imposition of sanctions for non-cooperation with a field investigation is politically unlikely, it is at least a possibility.

Field Investigation Report

Workshop participants agreed that the field investigation report prepared by the BWCO team should be factual and should include a technical assessment of the raw epidemiological data. Without interpretation, the scientific data are likely to be incomprehensible to international diplomats. For example, the report might be organized around the various competing hypotheses the team has pursued, summarizing the factual evidence for and against each of them. A concluding section would suggest which hypothesis is most likely, based on the evidence collected, without making a formal judgement of compliance. If a particular facility is implicated in the outbreak, the field investigation report could be made available in an expedited manner to the Executive Council for prompt action on whether there should be a transition to a facility inspection.

References

1. Matthew Meselson, Jeanne Guillemin, Martin Hugh-Jones, Alexander Langmuir, Ilona Popova, Alexis Shelokov, Olga Yampolskaya, "The Sverdlovsk Anthrax Outbreak of 1979," *Science*, 18 Nov. 1994, **266**, 5188, pp. 1202–1208**.**

2. As a practical matter, it can be difficult to differentiate between primary and secondary cases. Patients are usually termed secondary if they claim to have been in close contact with another sick individual, but since many victims typically do not know how they acquired the disease, some primary cases may actually be secondary and vice-versa.

3. If genetic engineering becomes an issue and DNA is available, one can identify parts of the genome of the suspect strain that differ from a reference strain. With that information, one can then sequence the differential regions of the suspect strain to see if there are inserted sequences or other telltale evidence of genetic engineering.

Transition to a Facility Investigation 5

The BWCO investigation team probably will not include many experts chosen for their expertise in facility investigations. Thus, if a specific facility is implicated in the outbreak, a separate team with different expertise will probably have to be constituted. This second team will presumably require a political mandate from the BWCO Executive Council, either as the result of a state-party request for a challenge investigation of the facility or a decision by the Executive Council to transition from a field investigation to a facility investigation. Thus, while it would be desirable to have a smooth segue from one type of investigation to another, that may not be logistically or politically feasible.

Decision to Approve a Facility Investigation

Workshop participants agreed that the evidence to justify the transition from a field investigation to a facility investigation should be "strong," but were unable to develop a set of criteria that would apply in all cases. There was consensus, however, that a higher standard of evidence is warranted to justify a facility investigation because it is inherently more intrusive and could put legitimate proprietary and national-security information at risk.

With respect to the workshop scenario, participants agreed that the epidemiological evidence for a non-natural origin of the outbreak—particularly the data suggestive of an aerosol release and pointing in the direction of two suspect facilities—is sufficiently compelling to warrant a facility investigation. In actual cases, however, the circumstantial evidence implicating a particular facility may be much weaker. As a result, it may be necessary to place greater reliance on declarations by the host country and intelligence information provided by member-states, while holding the latter to strict standards of evidence.

One workshop participant asked the group to consider the following situation. Six pharmaceutical companies are located in the Special Economic Zone north of the primary focus of the plague outbreak. The investigation team believes that one of these facilities is somehow linked to the plague outbreak, but cannot be sure which one. How should the team proceed? It would presumably be difficult if not impossible to secure Executive Council approval to inspect all six plants. Another participant

argued that for political reasons, it is unlikely that a BWCO investigation team will have a second chance to inspect a facility if the first visit yields negative results.

In response to this statement, a participant objected that epidemiology is the science of chance and uncertainty. If the team has only one opportunity to inspect a facility, the odds of finding the right answer would be poor, and this scientific concern should be considered during the negotiations. The first participant responded that because science is tainted by politics, it is an unfortunate fact of life that the BWCO investigation team would probably not receive a second chance.

Assuming that political pressures will severely constrain the number of facility investigations that a BWCO team can perform, the team will have to be quite confident that the epidemiological evidence points to a particular facility before requesting to inspect it. It will be important to provide an empirical basis for such a decision, particularly when the data are incomplete or ambiguous. Some participants suggested that the team might start by reviewing the host country's declaration of what is produced in the suspect facility and the manufacturing capabilities on hand. If the facility does not work with infectious agents and lacks the appropriate production equipment, chances are low that it is linked to the outbreak.

Another participant objected, however, that facility declarations by the host country could be misleading or incomplete, and that a declared facility engaged in clandestine BW agent production would almost certainly do so under civilian cover. Thus, if the team were to decide which facility to inspect based on declarations alone, it could easily be led astray. Here again, several participants stressed the importance of intelligence provided by states-parties to augment the host country's declaration and the circumstantial evidence uncovered by the epidemiological field investigation.

Use of Intelligence Information

Workshop participants agreed that intelligence information provided by states-parties would almost certainly be needed to buttress a facility investigation request. Intelligence-sharing is a complex matter, however, because of the need to protect sensitive sources and methods of collection. UNSCOM is the first international organization to work closely with the intelligence agencies of member-countries, but the relationship was difficult to establish and took years before it was operating smoothly.

Workshop participants discussed mechanisms by which intelligence information could be made available to the investigation team. For example, consider that Ripurna learns from a reliable intelligence source that the Westco pharmaceutical plant has a secret room hidden behind a false wall in which BW agents are allegedly being produced. If the Ripurnan authorities pass this information to the Executive Council *after* the decision has been made to approve a facility investigation, the council could presumably decide to inform the BWCO investigation team about the secret room. It might be politically unacceptable, however, for Ripurna to pass confidential intelligence directly to the investigation team without first channeling it through the Executive Council, even if the council had approved the request for a facility investigation.

Another participant suggested that if an observer from the requesting state-party accompanies the BWCO investigation team, he or she could provide additional information directly to the team leader during the investigation. The key requirement for ensuring the political neutrality of the BWCO would be for the investigation team to have the freedom to decide whether or not to act on the information provided. At the same time, the team will experience some pressure to demonstrate that it did a thorough job of investigating the compliance concerns. If the team

simply ignores the requesting state-party's advice and suggestions, that could reflect badly on the inspectorate.

Although one can make numerous arguments for and against specific intelligence-sharing arrangements, workshop participants agreed that the use of intelligence information should be permitted if the data are appropriately channeled and filtered. It would be unwise to exclude potentially valuable information after the Executive Council has approved a facility investigation. The policy challenge that remains to be addressed is precisely how to integrate sensitive intelligence information into a BWCO investigation.

Team Composition

A facility investigation team will need a variety of experts, including:

- A team leader who has both technical expertise and diplomatic training to negotiate managed access with officials from the host facility;
- An epidemiologist to reanalyze—and possibly to recollect—some of the data put together by the previous team;
- An industrial microbiologist or facility engineer to provide an understanding of fermentation equipment and building features such as ventilation systems;
- A veterinarian to assess a facility like the Nobutan Academy of Veterinary Sciences or disease symptoms in laboratory animals;
- A microbiologist specializing in the disease agent responsible for the outbreak and capable of analyzing environmental or biomedical samples;
- A team physician specializing in infectious diseases and familiar with prophylactic and therapeutic measures;
- A communications officer to maintain contact with BWCO headquarters;
- A biohazard specialist to assess containment and contamination issues;
- A bioweaponeer to assess weaponization technologies such as genetic engineering and microencapsulation;
- An operations officer to coordinate logistics; and
- Two or three interpreters and translators fluent in the host-country language.

Inspection Equipment

BWCO investigation teams will require a variety of inspection equipment, including devices for sample collection and analytical techniques such as ELISA (enzyme-linked immunosorbent assay) and PCR (polymerase chain reaction). In the event of a hazardous situation, the investigators will need to don personal protective equipment such as gas masks and protective clothing. The investigation team will also require logistical and support equipment, including a satellite telephone to maintain real-time contact with BWCO headquarters, fax machines, copiers, and walkie-talkies.

Mandate for a Facility Investigation

Participants agreed that the mandate of a facility investigation should be fairly broad, allowing the team to widen the scope of the visit if warranted. For example, the inspection site may comprise several buildings, including satellite structures that are geographically separate from the main site and may not be identified until later. If BWCO investigators notice a warehouse separate from the main plant, they should have the right to request an inspection. Permission to inspect satellite buildings would not be granted automatically but would be negotiated with the representative of the host facility.

One participant noted that whether the mandate of a facility investigation team includes checking the declaration of the inspected facility may depend on whether the BWC protocol creates a parallel process of random or clarification visits for checking the accuracy and completeness of declarations. If the finished protocol does not include a provision for such "non-challenge visits," the mandate of facility investigation teams might have to be extended to perform this function.

Investigation Timeline

Participants agreed that the BWC Compliance Protocol should define a timeline for access to a suspect facility and the conduct of an inspection. For example, the protocol would specify that the BWCO must notify the host country that the team is due to arrive at the point of entry in x hours. The host country would then transport the team to the inspection site in $x + y$ hours and grant access to the facility in $x + y + z$ hours. Participants estimated that a duration of 72 hours would be appropriate for a facility inspection but recommended the possibility of extensions if necessary, since inspecting a large site with multiple buildings could take longer. The main issue with timing is that it does not take long to "clean up" a facility and hide or destroy incriminating evidence or cultures. Because certain forensic evidence is time-sensitive, the sooner a team is on-site, the better. Other forensic evidence (e.g., DNA) decomposes slowly, however, so that telltale indicators are likely to remain for some time.

Conduct of a Facility Investigation 6

The objective of a facility inspection in the context of a field investigation is to obtain data that will enable the BWCO to determine the source of a suspicious outbreak. Workshop participants agreed that the investigation team should have a clear mandate from the BWCO defining its mission and objectives.

Perimeter Monitoring

During a facility investigation, it will be necessary to secure the perimeter of the site against unauthorized transfers of equipment or material, including the right to inspect vehicles entering or leaving the area. The bigger and more complex the site, with numerous entrances and exits, the more challenging the task of preventing someone from removing important evidence out the back door. Security does not necessarily mean physically controlling all access points but rather ensuring a way of "freezing" the situation in time and documenting what has happened. For example, the investigation team might place tags or seals on doors to determine if any movement of people or goods out of the building has occurred.

Managed Access

Workshop participants agreed that members of the investigation team must be adequately protected from biohazards at all times. The team must also be prepared to negotiate access with the host facility. This negotiation will entail an inherent tension between the facility's legitimate right to protect industrial trade secrets and the possible concealment of illicit biological-warfare activities.

In addition to securing the perimeter and seeking visual access to relevant areas of the facility, the investigation team may ask to audit production, shipping, and receiving records to correlate them with the facility declaration (if the facility has been declared). Copious amounts of records should be available that can be examined on a managed-access basis to reassure the team that what has been produced at the site was legitimate. The team may also wish to review safety and personnel records (e.g., to look for incongruous immunizations), standard operating procedures, emergency and safety procedures, and records of modifications made to the facility, especially with respect to ventilation or containment systems.

Most participants agreed that the host facility should have the right to manage access and should not have to submit to a *carte blanche* review of all its books and records. Instead, the inspectors would have to request data for a particular time period, with negotiated limits on access. Restrictions on access to personnel records might also be negotiated on privacy grounds. In general, seeking various types of corroborating information is the best way to determine that a facility's activities are legitimate.

Still and Video Photography

Unlimited use of still and video photography by the investigation team to document the production process would be objectionable to industry because it could compromise confidential proprietary information. A pharmaceutical company would probably be willing to show the team various parts of the production line to address any compliance concerns, but would prefer that such information not be broadcast to the world. Industry might be partially mollified if there were strict guidelines on who could see such videotapes and when they would be destroyed.

Although videotaping and still photography would not be cost-effective as routine investigation tools, they could be used to document major anomalies in a facility. Videotaping the collection of samples would also help to confirm that the samples were taken correctly and that chain-of-custody has been preserved. Another situation in which inspectors might use video cameras would be to monitor areas of a facility that are not easily accessible, either because they involve hazardous production processes or because they must be kept sterile to avoid contaminating the pharmaceutical product. In such cases, one team member might take a live video of a space that cannot be inspected directly, so that the entire team can observe the scene in real time. This video image would serve to corroborate other documentation, such as maps and standard operating procedures.

Conduct of Interviews

It would be desirable for the investigation team to interview a wide range of plant employees to permit the cross-checking of information from various levels of the organization (senior management, middle management, and technicians). That degree of access is unlikely, however, because of the pharmaceutical industry's concern that an untutored technician could inadvertently reveal trade secrets. Although this concern might be addressed by having a senior manager present during interviews with plant workers, some workshop participants expressed concern that personnel who revealed BWC violations might be exposed to retribution. At present, the rolling text of the BWC Protocol does not include whistleblower protections.

One participant noted that the United States has conducted four national trial visits at biodefense-related facilities. A lesson learned from three of the four exercises was that interviewing non-managerial personnel can lead to inconsistent answers, increasing ambiguity and inappropriately undermining the investigation team's confidence that a facility is compliant with the BWC. This finding suggests that interviewing can be a double-edged sword.

Sampling and Analysis

During a facility investigation, the BWCO team should be able to take biomedical specimens such as blood and urine from laboratory animals on-site and possibly from plant workers, although legal and political obstacles may prevent involuntary biomedical sampling. In addition, the team will wish to take swipe samples from laboratory benches, work stations, fermentation equipment, and air-filtration systems.

Environmental sampling of soil, biota, and waste water near the plant would be politically acceptable, although the results may be ambiguous.

Workshop participants discussed whether the facility investigation team should have the right to perform its own on-site sampling and analysis. The consensus was that host-country escorts could monitor the inspectors on a one-to-one basis to ensure that no unauthorized sampling occurs. In most cases, the team would probably bring its own reagents and DNA probes for on-site analysis. At more sophisticated facilities, however, company employees should be allowed to take the samples and conduct the analysis with the facility's own equipment, under the close observation of the investigation team.

Participants agreed that the facility investigation mandate should permit testing only for the specific agent linked to the suspicious disease outbreak, rather than any known biological-warfare agent, to preclude "fishing expeditions." In the workshop scenario, the WHO team has already identified the strain of plague responsible for the outbreak and the BWCO team is trying to determine its source. Thus, the latter team would not need to engage in broad-based sampling but would search instead for a particular strain of *Yersinia pestis*.

It was pointed out, however, that the investigation team may not always know precisely what strain to look for during a facility investigation. By the time the BWCO team arrives in a country of concern, the epidemic may be over and the team may not have access to clinical samples from sick patients. As a result, the team would not be able to determine the unique genetic characteristics of the outbreak strain that would be needed to design an assay for genetic markers, such as the unique DNA sequences associated with antibiotic resistance.

Workshop participants assumed that sampling bulk raw materials and products would be acceptable to industry but that sampling the contents of fermentors could put confidential proprietary information at risk. In virtually all cases, however, samples can be analyzed on-site with the facility's own equipment or assays brought along by the team. Future teams might even employ disposable analysis kits, either antibody-based or DNA-based, that can be left behind or destroyed after use. This approach would minimize host-facility concerns that team members might engage in industrial espionage by recovering proprietary DNA sequences from used analytical equipment.

A few samples may require off-site analysis. Certain toxins, for example, can only be identified with sophisticated analytic techniques such as mass spectrometry. Although genetic identification of microbial strains with PCR (the polymerase chain reaction) can be performed on-site, this method is not yet highly reliable or consistent. Because of the high rate of false negatives and false positives in the field, most diagnostic laboratories in the world that perform PCR generally insist on taking specimens back their home facilities for definitive analysis.

The Meaning of Sampling

The United Nations Special Commission (UNSCOM) charged with eliminating Iraq's biological and other weapons of mass destruction has found that sampling is a potentially valuable technique if used selectively. Before taking samples, the investigation team should have a good scientific reason for doing so. There is no point in taking a sample unless a positive analytical result is meaningful and can be interpreted unambiguously. For example, the team must be confident that a positive result is not the result of environmental contamination, particularly if the agent in question is indigenous to the area. If a sample is taken from inside a fermentor, inadvertent contamination is quite unlikely. In contrast, taking a swipe sample from a

floor or a benchtop in a microbiology laboratory is less useful because of the greater probability of environmental contamination, making a positive result more difficult to interpret. Indeed, if anthrax spores are found, a skeptic could argue that plant workers had brought them into the laboratory on their shoes. As one participant observed, sampling that provides no definitive information is "worse than useless." Several participants suggested that the investigation mandate should require that sampling be performed only when it is scientifically warranted, putting the onus of responsibility on the team.

In the workshop scenario, the WHO investigation team uses genetic analysis and antibiotic susceptibility testing to identify the strain of plague that caused the outbreak in Nobuti. These tests reveal that the strain contains specific DNA sequences corresponding to plague virulence factors and antibiotic resistance genes. Later on, the facility investigation team uses PCR to analyze swipe samples taken from laboratory benchtops inside the Academy of Veterinary Sciences, and identifies the same strain of *Yersinia pestis*. The latter results are ambiguous, however, because the plague outbreak occurred in close proximity to the veterinary school. If the disease outbreak were of natural origin, it would not be surprising for scientists at the school to collect samples and try to isolate the causative agent. Thus, the mere detection of plague inside the facility does not constitute a "smoking gun" that the facility was deliberately producing plague for biological warfare purposes.

The BWCO team also draws some unwarranted conclusions from its PCR analysis. Since the DNA sequences indicative of a virulent, antibiotic-resistant strain of plague are all present in one sample, the team assumes that they are all from the same bacterium, but that is not necessarily the case. From PCR analysis alone, it is not possible to determine whether the sample contains a deadly strain of plague containing the full panoply of virulence and antibiotic-resistance genes, or a mixture of relatively harmless bacteria. For example, the sample might actually contain a benign vaccine strain of *Yersinia pestis,* which would be detected by the chromosomal DNA probe, and a soil bacterium that has incorporated a transmissible antibiotic-resistance plasmid, which would be detected by the plasmid probe. To demonstrate that all of the characteristic DNA sequences are present in the same bacterial genome, it is first necessary to grow the agent in culture before proceeding with a detailed genetic analysis.

Unfortunately, culturing plague bacteria with traditional methods is difficult and time-consuming. David Dennis's "A Primer on Plague" (Appendix A) indicates that it generally takes three days before *Yersinia pestis* colonies grow large enough to be suitable for analysis. Thus, the investigation team would have to remain on-site for at least 72 hours just to confirm the identification of the disease agent. One possible option would have the inspection team work in shifts on a 24-hour basis. Alternatively, the inspectors could streak the agar plates (i.e., the Petri dishes containing bacterial culture medium) and leave them on the laboratory bench with a video camera to deter tampering. If, however, the cultures fail to grow or are contaminated with other bacteria, it is unlikely that the team would have a second chance to do the analysis. Finally, it was pointed out that if Nobuti had developed a wild-type, indigenous strain of plague as a biological weapon, there would be no unique genetic markers associated with it.

Off-Site Analysis

The vast majority of facility investigations will not require taking samples off-site for analysis. Off-site analysis may be warranted, however, when the investigation

team uncovers significant anomalies, such as a major discrepancy between the characteristics of the production microorganism that a facility has declared and what is actually found in samples collected and analyzed on-site. The antibiotic-sensitivity of a microbial strain is easy to determine, and any vaccine plant should be capable of doing a fairly sophisticated restriction map ("genetic fingerprint") that provides clear evidence of antibiotic resistance. If, for example, the strain sampled at a vaccine plant turns out to be multidrug-resistant, that would constitute a major discrepancy with the facility declaration.

The discovery of an anomalous strain at a suspect facility would give the BWCO team valid grounds to conduct genetic subtyping, that is, to determine the DNA sequences associated with unusual types of antibiotic resistance. Since only a few sophisticated reference laboratories in the world can perform this type of genetic analysis, the samples would have to be taken off-site. In such cases, the team must maintain and document strict chain-of-custody procedures to ensure that the samples are not contaminated en route.

Industry Concerns About Proprietary Information

The biopharmaceutical industry's chief concern about receiving inspections is whether plants can be open and transparent enough to demonstrate that their activities are consistent with the stated purpose, while still protecting legitimate confidential proprietary information (CPI). Just because an inspected facility does not want sensitive information to leave the site does not necessarily mean that it is seeking to obstruct the inspection process. Beyond the need to protect trade secrets, access to certain areas of a plant may have to be restricted because of safety hazards or because entering a sterile area could breach Good Manufacturing Practice (GMP) standards and spoil a large batch of valuable product. To reduce suspicions, facility managers should explain clearly to the BWCO investigators why they cannot be granted full access.

In practice, however, trial visits conducted by the U.S. government at pharmaceutical plants and biodefense facilities have found that based on how the host facility reacts to inspector queries and requests for access, it can be difficult to distinguish between efforts to safeguard legitimate proprietary information and an attempt to conceal illicit BW activities. A workshop participant also worried that in the event a U.S. company is challenged, it would probably come under tremendous pressure from the government to give the inspectors free rein.

Nevertheless, a number of participants argued that a workable balance is possible between effective compliance monitoring and the protection of CPI. If the investigation team uses a little ingenuity, it should be able to negotiate its way to an approach that satisfies its compliance concerns without jeopardizing the inspected facility's legitimate trade secrets. In general, companies can readily share with the investigation team a large amount of information that does not involve proprietary data. Moreover, experience in Iraq and elsewhere has shown that illicit facilities are often unable to create a coherent scientific, technical, or defense-related argument to explain anomalies and discrepancies, even though they may have plenty of time to prepare elaborate cover-stories.

The pharmaceutical industry's chief concern with respect to protection of CPI is the off-site analysis of samples. Companies worry that removing a genetically engineered production microorganism to an outside laboratory and performing an analysis of its genetic structure would pose a serious risk of compromising valuable proprietary data. A workshop participant suggested, however, a possible compromise formula that might be acceptable to both

industry and the BWCO inspectorate. In return for giving the investigation team the right to take samples from the process stream (including from fermentor valves and flanges) and to employ its own assays, the team would have to specify in advance what agent(s) it was testing for, and the analysis would be performed on-site by host-facility employees under the team's supervision. In addition, all assays would be validated with the company's own culture medium, together with positive and negative controls, so that the investigation team is made aware of the likelihood of false positives or false negatives.

Facility Investigation Report

Workshop participants suggested that during and after a facility investigation, the BWCO team should prepare three types of reports: (1) a daily situation report to the BWCO Technical Secretariat; (2) an interim report prepared immediately after the inspection ends; and (3) a final report. The daily situation reports will contain sensitive operational data and hence should be kept confidential, although the findings in these reports can be summarized in the interim report. If possible, the team should issue its interim report before leaving the country, so that the inspected party has a chance to respond to it and request corrections of fact. Finally, after the data have been analyzed, the team will issue a more comprehensive final report for distribution to all states-parties.

An important issue is whether the final report should include a preliminary technical assessment of the team's findings or should merely present the raw data to the BWCO Technical Secretariat and the member-states for their interpretation. Some workshop participants argued that the team should only report factual observations in a set of technical annexes, along with any incidents of obstructionism on the part of the host country. Other participants countered that simply reporting raw epidemiological data without an accompanying scientific assessment would make the report incomprehensible to diplomats and government officials. For this reason, workshop participants agreed that the team should report the facts along with an objective scientific interpretation.

For example, the report might present a set of alternative hypotheses for the source of the outbreak and then make a judgement about which hypothesis best fits the evidence. The team might conclude, for example, that the probability of one hypothesis is 20 percent while that of the competing hypothesis is 40 percent. Experience with outbreak investigations has shown that when the team writes a detailed description with some scientific evaluation of the data, the report more or less speaks for itself. If the team encountered serious obstruction from the host country and was therefore unable to collect sufficient data, that finding would also imply that something was seriously amiss.

A possible model for the facility investigation report is the "Shooter Report," a formal investigation conducted by a distinguished scientific panel into an accidental outbreak of smallpox at Birmingham University Medical School in 1978, in which two people became infected and one died. The authors laid out several hypotheses for how the outbreak could have happened, which they then proceeded to test against the data. At the end of the report, having clearly examined all of the evidence, they came to a conclusion about the likely cause of the exposure.

Workshop participants agreed, however, that the largely political process of assessing compliance on the basis of the scientific evidence should remain the responsibility of member-states. Indeed, since countries are jealous of their prerogatives, it is likely that the BWC Protocol will sharply restrict the authority of the investigation team, as well as the BWCO and its director-general, to interpret the inspection results.

Compliance Assessment 7

The purpose of a field investigation under the BWC Protocol is to establish not only what happened to cause a suspicious outbreak of disease but to assess the likelihood that the outbreak could have occurred naturally. Given the specifics of the workshop scenario and the results of the field and facility investigations, the epidemiological evidence indicates strongly that the plague outbreak in Bisfah was a highly unusual event. If the investigation team is confident it has not missed many early cases, then the clustered geographical distribution of the victims, the explosive epidemic curve, and the detection of an unusual antibiotic-resistant strain of plague are all suggestive of a non-natural etiology.

Nevertheless, the epidemiological findings do not point to any particular perpetrator, nor do they provide proof that a BWC violation has occurred. Even if the team interpreted the unusual epidemic curve, geographical map, and agent strain to constitute unequivocal evidence of airborne exposure, that finding would not prove that the Nobutan government was the source of the release.

The facility investigation has also failed to uncover a "smoking gun." According to the scenario, characteristic DNA fragments from a strain of *Yersinia pestis* identical to the one isolated from the victims of the outbreak were found on laboratory benchtops at the veterinary school. It is not known, however, how the DNA came to be there. Conceivably, it could have been carried into the lab by an infected worker, to mention one of several possible explanations.

Although there is evidence that the desktop fermentors at the Academy of Veterinary Sciences were cleaned shortly before the inspection, it is unclear whether this fact indicates an attempted cover-up. It might just as easily be explained by standard laboratory decontamination procedures. Moreover, while the pattern of obstruction on the part of the Nobutan government is troubling and may indicate an effort to conceal illicit activities, it is hard to determine what exactly is being concealed—legitimate trade and military secrets or a clandestine biological-warfare program.

Given the failure of the facility investigation to yield a "smoking gun," the source of the outbreak remains ambiguous. Even if an accidental release of plague did occur from the Academy of Veterinary Sciences, a facility operated by the Nobutan government, the intent behind the production of

Yersinia pestis is unknown. Indeed, although the 1979 anthrax outbreak in the Soviet city of Sverdlovsk was linked conclusively to an accident at a military microbiological facility, it still remains to be determined whether the Soviets were violating the BWC by engaging in large-scale production of anthrax for offensive purposes, or whether they were using small amounts of the virulent agent to test the effectiveness of anthrax vaccine in laboratory animals—a defensive activity permitted by the treaty.

In sum, the evidence in the workshop scenario is suggestive but ultimately inconclusive. If the epidemiological data and analyses are correct, it is possible to conclude that a genetically modified form of *Yersinia pestis* was released as an aerosol from the veterinary school at a particular point in time, but with little certainty as to perpetrator or intent. To clarify issues of BWC compliance, the investigation team would have to pursue a set of forensic questions—namely motive, means, and opportunity.

Credible Epidemiological Evidence

It is important to examine the additional types of epidemiological data that would make the BWCO investigation team highly confident that this outbreak was not a natural event, even if the team was unable to determine who was responsible. First, if the team were to find epidemiological evidence similar to that in the workshop scenario but involving a non-indigenous pathogen such as Venezuelan equine encephalitis, that would almost certainly not be a natural occurrence, especially in an urban setting. In the workshop scenario, however, the outbreak involved an area of Nobuti where plague has occurred in the past, making it much more difficult for the team to conclude that the disease had resulted from anything other than natural causes.

Second, strong evidence for a BWC violation would exist if the team determined by genetic analysis that the type of plague that caused the outbreak was a reference catalogue strain that had caused epidemics at a previous historical time and place but no longer existed in the natural environment.

Third, another strong indication that the outbreak was of non-natural origin would be if the team determined from genetic analysis that the strain of *Yersinia pestis* had been deliberately engineered for enhanced virulence or environmental persistence, or if the investigators found four or five different strains of the agent in a single patient. For example, PCR analysis of biomedical samples taken from outbreak victims at Sverdlovsk showed multiple anthrax strains in almost every individual.

Scientific Versus Legal Standards of Proof

Legal standards for proving causation tend to be very different from public-health standards. Field epidemiologists work by collecting all of the available evidence and then piecing together a scenario that best fits the data, yet they rarely if ever find a "smoking gun." For this reason, epidemiological investigations often generate an overwhelming preponderance of evidence but rarely yield proof that meets the criminal-law standard of "beyond a reasonable doubt." For example, CDC has investigated suspicious clusters of hospital deaths in which the epidemiological data strongly suggested that one person was responsible. Yet criminal cases based on statistical evidence are often thrown out of court because the investigators cannot prove absolutely that the suspect committed the crime.

The same political difficulties exist in an arms control compliance setting such as this one. Quite often, a conclusion that is scientifically valid does not meet the diplomatic, political, or legal standard of proof. In the workshop scenario, the BWCO investigation

team finds a preponderance of scientific evidence indicating that the outbreak in Bisfah was an non-natural event, but they were obviously not present at the veterinary school at 12:17 a.m. on September 15 to observe exactly what happened. Was there an accident at an illicit biological weapons production facility? Or did a disgruntled graduate student angry over a bad grade open a vial of plague bacteria and throw it into a laboratory exhaust vent? It is impossible to know from the available information.

Skeptics may also raise methodological questions about the provenance of the outbreak strain. In the workshop scenario, the WHO investigation team presumably did not follow the strict chain-of-custody procedures required when collecting samples in criminal investigations. Even if the BWCO team subsequently follows strict forensic procedures in isolating plague from the Academy of Veterinary Sciences, it might not be possible to conclude definitively that this strain is identical to the one that WHO isolated earlier from the sick patients in Lanaville. Indeed, even if the conclusion that the strains are the same is scientifically reasonable, it might not meet a more rigorous legal or diplomatic standard of proof. A lawyer could argue, for example, that because of the lack of chain-of-custody for the WHO clinical samples, it is possible that a Ripurnan operative used a strain from an existing culture collection to blackmail the Nobutan government.

According to a workshop participant who practices medicine, the task of diagnosing rheumatoid disorders offers a useful analogy to assessing BWC compliance. Unlike infectious diseases, which can be diagnosed by culturing the causative agent from a body fluid, rheumatoid diagnoses (with the exception of gout) are all inferential. Over time, practicing rheumatologists typically accumulate experience and establish an ever-higher odds ratio for making an accurate diagnosis based on descriptive criteria. Assessing BWC compliance is similar. The BWCO inspectorate will hardly ever find a "smoking gun," such as a rack of filled biological munitions. Rather, the BWC compliance regime will simply accumulate data over time, building an ever-stronger case that never arrives at 100 percent certainty because there is no gold standard.

In sum, the scientific process of determining whether a disease outbreak is a deliberate or a natural event is separate from whether the evidence would hold up in a court of law. In this case, the BWCO is not trying to persuade a jury but rather a group of diplomats and government officials. The best the BWCO will ever be able to accomplish is to compile scientifically credible evidence. In many cases, the evidence will speak for itself, indicating strongly that something seriously anomalous has taken place. But high politics will take over when states-parties make their own compliance judgements.

Like beauty, treaty compliance is in the eye of the beholder. Regardless of the nature of the scientific evidence, compliance judgements will differ among individual states based on their specific political, economic, and military perspectives. Countries that have political reasons to deny or disbelieve an allegation will develop excuses and counter-explanations, while countries that are inclined to believe the scientific evidence will take whatever punitive or defensive measures they consider appropriate.

Appendix A: A Primer on Plague

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Plague is an ancient disease that continues to claim victims today. From 1981 through 1995, 25 countries in Africa, the Americas, and Asia reported a total of 21,087 cases of plague and 1,932 deaths (10 percent). The cause of this disease is *Yersinia pestis*, a bacillus in the family of bacteria known as Enterobacteriaceae. Plague has achieved a toehold in many parts of the world by infecting wild burrowing rodent populations, and it is also present in domestic rats and their fleas in cities and other settings where rodents live in close association with humans (**Figure 1**).

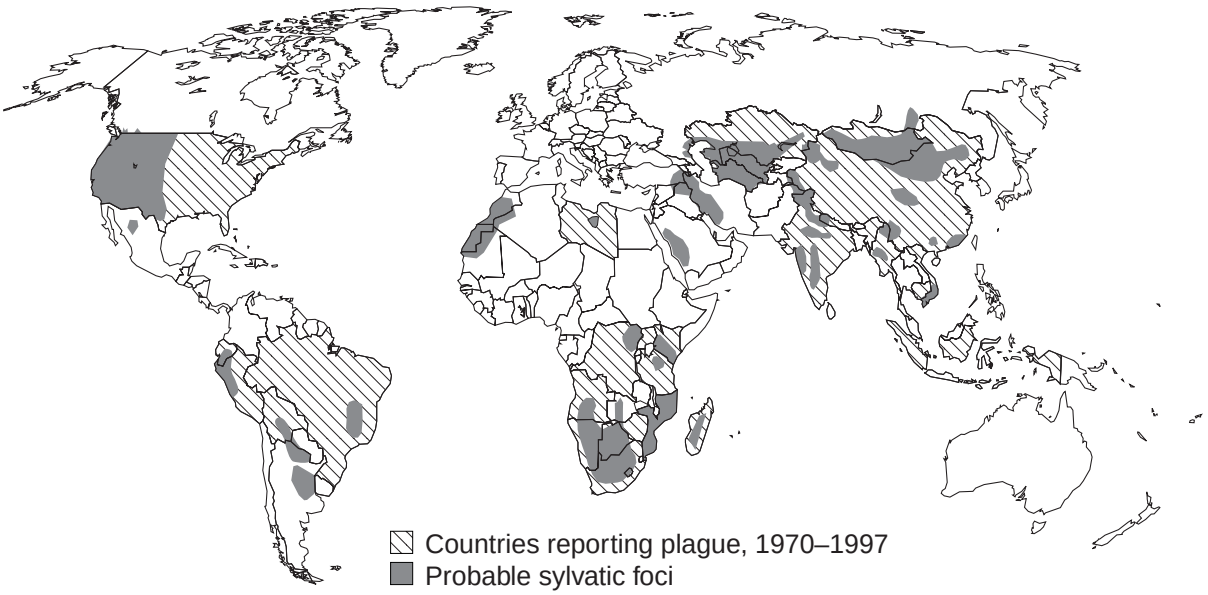
The Three Pandemics

Plague is the prototypical reemerging disease. Scattered throughout the world are three basic strains of *Yersinia pestis*.[1] Termed *antiqua*, *medievalis*, and *orientalis*, these strains relate to the three major pandemics of plague that have occurred over human history. The *antiqua* strain was associated with the Justinian Pandemic of the 6th and 7th centuries, which spread from Central Africa into Egypt and then moved along the Mediterranean littoral into the Middle East and finally into parts of Europe. Today the *antiqua* strain can still be found in Africa and Central Asia.

The *medievalis* strain was associated with the Black Death, or Medieval Pandemic, which originated in Central Asia, invaded Europe in about 1347, and spread there in epidemic waves. It finally disappeared in the early part of the 1800s, although the *medievalis* strain persists today in foci around the Caspian Sea.

The *orientalis* strain caused the modern or Third Pandemic, which began in Yunan province in southwestern China and spread into Hong Kong in 1894. Steamships carried the disease from Hong Kong to ports around the world, first to Bombay, India, in 1896, and then to Africa, South America, and North America. Over a period of about 10 years, plague spread to every inhabited continent. India was hardest hit by the Third Pandemic, with an estimated 26 million cases and about 12 million deaths between 1896 and 1926.

After the 1920s, plague epidemic activity dwindled because of several factors, including improved sanitation and hygiene, the extermination of rats in ports and on ships, the increasing use of insecticides to control fleas, and an improved public-health infrastructure. Even so, in the late



Compiled from WHO, CDC, and country sources.

Figure 1. Global Distribution of Plague.

1940s and early 1950s, tens of thousands of cases of plague were reported each year, mainly in India.

After a period of minimal epidemic activity in the late 1950s and early 1960s, plague made a comeback. An epidemic occurred in Vietnam in 1965–75 during the war period, and several other outbreaks have been reported elsewhere over the past two decades. In the early 1990s, there were about 2,000 human plague cases in Peru, and an outbreak occurred in the city of Surat, India, in 1994. Over the last few years, higher-than-usual levels of plague have been reported in Yunan province in China (where the Third Pandemic began) and in several areas of eastern Africa. In February–March 1998, a small outbreak of pneumonic plague took place in Ecuador.

The growing incidence of plague in Africa has been primarily responsible for the six-fold increase in the number of cases throughout the world since 1980 (**Figure 2, Table 1**). A large outbreak occurred in Tanzania in 1991 and again in 1995. In Madagascar, in addition to rat-borne plague in the rural highlands, several outbreaks of urban rat-borne plague have been reported since 1995 in the port city of Mahajanga. Because of the extensive small-boat (*dhow*) trade along the African coast, epidemiologists have worried that plague could spread to other port cities, but to date there is no evidence of this.

Distribution in the United States

Plague is endemic in the western regions of the United States. The disease was introduced into San Francisco in 1899, and the first indigenous human case occurred there in 1900. Two epidemics between 1900 and 1910 sickened several hundred people. Having infected the urban rats of San Francisco, the disease spread into the wild burrowing rodent population in surrounding counties. It then moved into other parts of California and into Oregon. Outbreaks of human plague occurred in Oakland in 1919 and Los Angeles in 1924. Thereafter, plague in the United States became a rural disease, with sporadic cases arising in individuals who had contact with infectious wild ro-

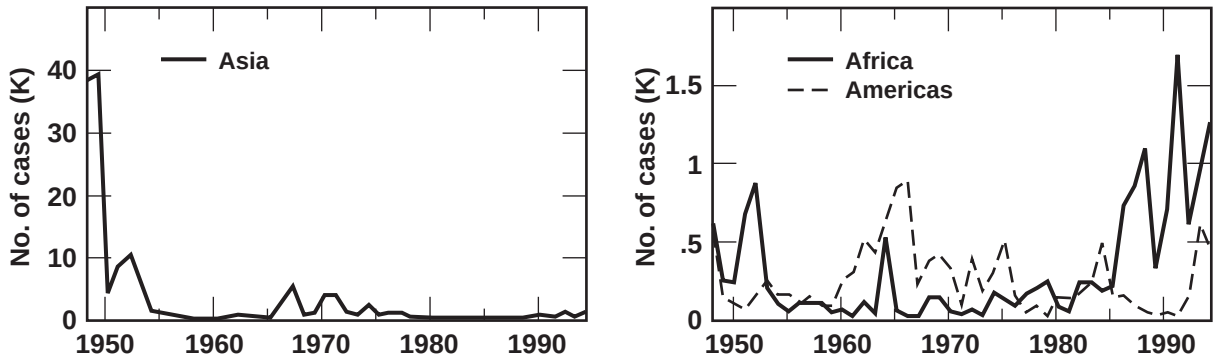


Figure 2. Plague cases notified to WHO in Africa, the Americas, and Asia, 1948–1994.

dents or their fleas, and sometimes with the infectious tissues of wild carnivores, hares, and rabbits.

During the first two decades of the 20th century, plague was introduced to port cities along the Gulf of Mexico and the Seattle area but never attained a foothold in the wild rodent populations there, making it fairly easy to control. In contrast, in Hawaii the disease persisted for several decades and was only considered eradicated in the 1950s.

Since 1944 there has been an increasing number of plague cases per decade in the United States, as well as a growing number of states reporting cases. In the 1960s, human plague activity increased in the Four Corners area of the U.S. Southwest. An outbreak there in 1983–84 was preceded by heavy rainfall associated with an El Niño weather pattern in the early 1980s, and since then the disease has maintained itself in the area. Today, plague infects wild-animal populations throughout the western United States and the Great Plains eastward to about the 100th meridian. Some signs of animal plague activity have been reported in North and South Dakota, Nebraska, and more recently in Kansas and eastern Texas. In 1993, plague was found in a few urban rodents in Dallas, but conditions there were not conducive to its spread.

Natural History of Plague

The natural history of plague involves two basic mechanisms of transmission (**Figure 3**). In the "urban cycle," the domestic rat (*Rattus rattus*) and the sewer rat (*Rattus norwegicus*) carry the disease, which is transmitted to humans by their fleas, especially the oriental rat flea (*Xenopsylla cheopis*). In the "sylvatic cycle," the disease cycles among wild burrowing rodent species such as prairie dogs and ground squirrels, and is transmitted by their fleas, most of which are specific to the wild rodent hosts.

In both the urban and the sylvatic cycles, fleas carry the disease from the infected animals to humans. The blood meal in the midgut of the flea serves as a medium for plague bacteria to grow and reproduce. The bacteria multiply to the point where they block the esophagus of the flea, making it starved for further blood meals. When the flea then tries to feed, it may regurgitate a bolus of infected blood into the host, enhancing the transmission of plague bacteria.

Humans can be infected by fleas involved in the urban or sylvatic cycle, or by direct contact with infected animals in those cycles. In addition, plague can spread directly from person to person by the respira-

Table 1. Reported cases of plague in humans by country, 1981-1995.

Continent	Country	No. of cases	No. of deaths
Africa	Angola	6	0
	Botswana	173	12
	Democratic Rep Congo (Zaire)	2,824	536
	Kenya	44	8
	Libya	8	0
	Madagascar	2,526	323
	Malawi	9	0
	Mozambique	216	3
	South Africa	19	1
	Tanzania	5,746	482
	Uganda	660	48
	Zambia	1	1
	Zimbabwe	397	31
	Total	**12,629**	**1,445**
Americas	Bolivia	163	25
	Brazil	611	9
	Ecuador	83	3
	Peru	1,819	114
	United States	220	29
	Total	**2,896**	**180**
Asia	China	230	56
	India	876	54
	Kazakhstan	10	4
	Laos	7	0
	Mongolia	58	20
	Myanmar	1,087	10
	Vietnam	3,294	163
	Total	**5,562**	**307**
World Total		**21,087**	**1,932**

tory route. Humans are incidental, dead-end hosts of plague except for those circumstances in which there is respiratory spread. A number of virulence factors carried on plasmids (small circles of non-chromosomal DNA) can enhance the ability of *Yersinia pestis* to infect and cause disease in humans.

Some fleas are more efficient transmitters of plague than others. In the United States, the species of flea that infests rock squirrels also feeds on and can infect other rodents that live in the vicinity of humans,

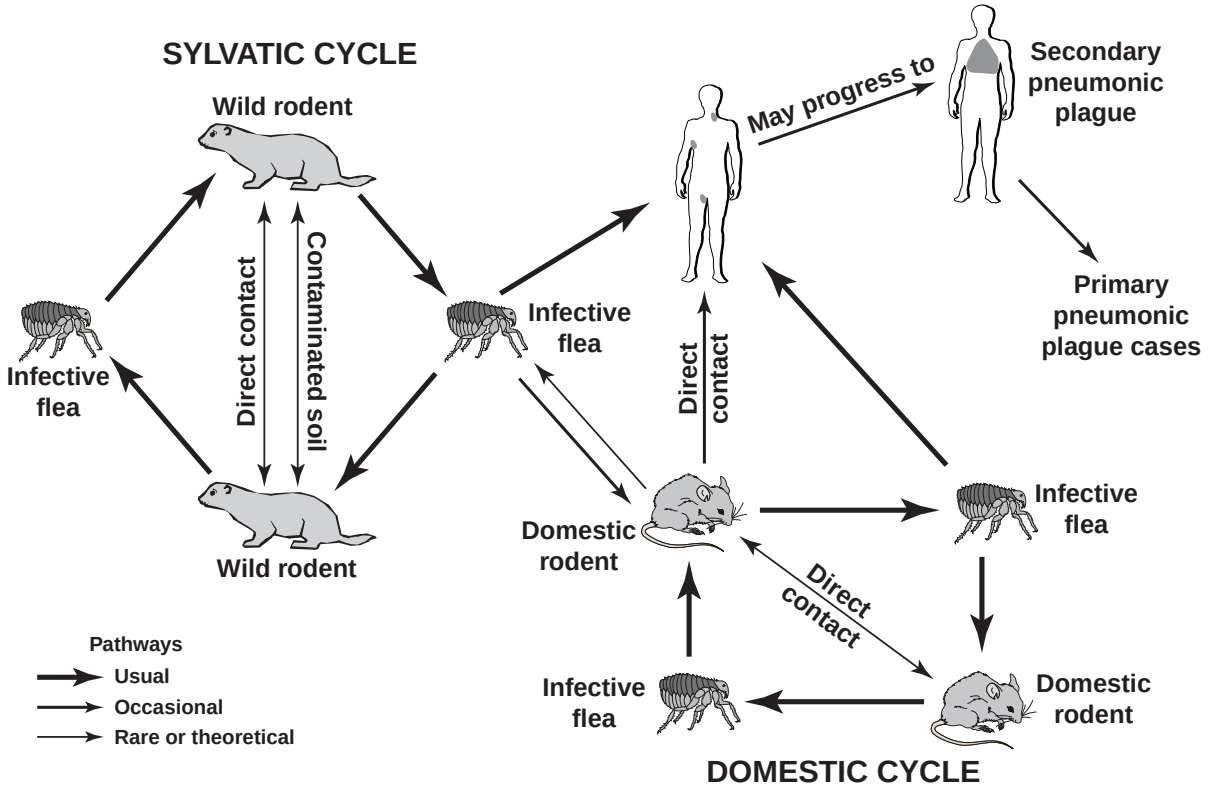


Figure 3. Plague cycles.

as well as domestic dogs and cats. These fleas also bite humans. In contrast, a number of sylvatic cycles involve fleas that almost never bite humans, making them poor transmitters of disease. In Africa and India, the wild rodent hosts of plague often come into contact with rodents living in fields adjacent to and within villages. In this case, the same species of plague-infected flea feeds on animals in both settings.

Principal Clinical Forms of Plague

The incubation period of plague is two to six days, although there have been reports of incubation periods as short as one day and as long as 10 days. Initial symptoms of infection are usually nonspecific: fever, chills, headache, and severe muscle and joint pain. Prostration is a common feature of the disease: after two or three days of infection, most patients are bedridden.

Human patients develop three principal forms of plague: bubonic, septicemic, and pneumonic. The most common form is bubonic plague, characterized by the infection and swelling of the regional lymph nodes draining the site of inoculation by an infected flea. The swollen lymph nodes are known as "buboes," and sometimes a small skin ulcer is present at the site of the flea bite. A typical patient with bubonic plague is acutely ill and has enlarged lymph nodes in the groin, the upper inner thigh, or the underarm region. Less commonly, buboes occur in the neck. Buboes can be either unifocal, typically affecting the lymph nodes closest to the flea bite, or multifocal, resulting from the spread of plague bacteria through the bloodstream. Plague buboes distinguish themselves from most other causes of swollen lymph nodes by being exquisitely tender. Patients guard against

palpation of the buboes and avoid any movement of the affected area because of this extreme tenderness.

Septicemic plague develops when *Yersinia pestis* invades and multiplies in the patient's bloodstream. Primary septicemic plague results from the direct inoculation of the bacteria into the bloodstream and their subsequent multiplication without the formation of buboes. Secondary septicemic plague typically begins with the bubonic form of the disease, after which the bacteria spread into the bloodstream and multiply. Before patients are given antibiotics, plague bacteria can be isolated from blood cultures in about 70 percent of cases.

The first symptoms of septicemic plague include nausea, vomiting, diarrhea, and abdominal pain. In the United States, many patients with septicemic plague are not diagnosed immediately because there are no localized signs and the disease appears to involve the gastrointestinal tract. Septicemic plague is often associated with a dramatic set of complications known as systemic inflammatory response syndrome. Symptoms include disseminated intravascular coagulation (clotting of the blood within blood vessels, interrupting the flow of oxygen to the tissues and sometimes resulting in gangrene of the fingers and toes), adult respiratory distress syndrome, shock, and organ failure.

Finally, patients may present with pneumonic plague if they have inhaled respiratory droplets containing plague bacteria emitted by an infected human or animal. Pneumonic plague is associated with cough, shortness of breath, bloody sputum, and evidence on X-ray of lung infiltration.

In the United States, more than 85 percent of plague cases are bubonic and result from the bite of an infected flea. About 10 percent of cases are septicemic, some resulting from direct contact with infected tissues. Less than 5 percent of cases involve primary pneumonic plague. Other rare forms of the disease involve the pharynx (throat) and the meninges (the membranous coverings of the brain).

Forms of Pneumonic Plague

With *primary* pneumonic plague, the mode of transmission is by inhalation of infective respiratory droplets. Unlike tuberculosis, measles, or smallpox, in which the microorganism can form a respirable aerosol, *Yersinia pestis* does not aerosolize under natural conditions. Coughing by an infected individual generates respiratory droplets containing plague bacteria, which are fragile and do not survive for long in the atmosphere. As a result, exposed persons only become infected if they are in close proximity to an individual suffering from pneumonic plague, usually within two or three meters. Since 1924, all cases of primary pneumonic plague in the United States have arisen from exposure to infected domestic cats.

The incubation period of primary pneumonic plague is normally from one to four days, rarely longer. The bacteria multiply in the alveoli (tiny air sacs) of the lungs, and the resulting inflammation gives rise to severe edema (accumulation of fluid in the tissues). If the disease runs its course, the victim will eventually "drown" in his or her own secretions. Coughing generates contagious respiratory droplets that can infect other individuals. The sputum is typically watery and may be blood-tinged or quite bloody.

Presenting symptoms of primary pneumonic plague include fever, headache, muscle aches, weakness, tightness and pain in the chest, cough, and shortness of breath. On chest X-ray, the disease presents as a lobular pneumonia, which rapidly extends to the rest of the lungs in less than 24 hours, leading to the development of acute respiratory distress syndrome. Primary pneumonic plague induces extreme prostration: patients usually lie motionless in bed unless they become so air-hungry that they become agitated. Other complications include systemic inflammatory response syndrome. Primary pneumonic plague has

a very high fatality rate if it is not treated within 24 hours of onset.

Secondary pneumonic plague may arise as a complication of bubonic or septicemic plague if the infection spreads into the lungs. This form of the disease may be delayed until days after the initial illness manifests itself. In rare cases, plague bacteria first lodge in the pharynx, giving rise to local inflammation and pharyngeal buboes, after which the infection extends directly into the lungs and causes pneumonia.

Secondary pneumonic plague progresses more slowly than primary pneumonic plague and involves the interstitial tissues of the lung rather than the alveoli. The sputum is scant, non-watery, and frequently blood-streaked. Cough is usually less prominent than in primary plague pneumonia, possibly because patients with secondary pneumonic plague have been sick longer and hence are less able to mount a vigorous cough reflex. Secondary pneumonic plague generally has a higher survival rate than the primary form of the disease, but systemic inflammatory response syndrome and its complications may intervene.

Epidemiology of Pneumonic Plague

Outbreaks of pneumonic plague are rare. This form of the disease certainly occurred during the Medieval Pandemic but was not well documented. Beginning with the Third Pandemic at the turn of the century, there have been a few well-recorded outbreaks of pneumonic plague. The largest of these occurred in Manchuria in 1910–11 and 1920–21. These epidemics took place under unusual circumstances: people were crowded together in boxcars and small shacks in the middle of winter in subzero temperatures. The high humidity and overcrowding provided optimal conditions for the viability of plague bacteria in respiratory droplets, so the disease spread rapidly from person to person.

Two small outbreaks of pneumonic plague occurred in the United States in Oakland in 1919 and Los Angeles in 1924. An outbreak in Ecuador took place in 1939 and recurred in precisely the same area in early 1998. In India, a rather large pneumonic plague outbreak involving some 1,400 people took place in 1911, but the pneumonic form of the disease did not reappear there until 1948–49. A poorly documented outbreak of pneumonic plague took place in Surat, India, in 1994.

In Tanzania in 1991, an outbreak of pneumonic plague arose when an individual living in a rural area of the country became infected and traveled to the capital city of Dar es Salaam, where he infected householders with whom he was staying. These people were admitted to the hospital and in turn infected health-care providers and others with whom they came in close contact. Thus, even today, pneumonic plague can be introduced by a traveler into an urban area where plague is not endemic.

Most outbreaks of pneumonic plague are fairly short-lived. One or two primary cases can infect a large number of secondary cases, but the disease is so severe that after one or two cycles of transmission, people are hospitalized and the illness is diagnosed. Transmission stops once the infected patients have been placed under isolation and managed using respiratory precautions.

The last outbreak of pneumonic plague in the United States took place in Los Angeles in 1924 and involved 30 cases. During the period from 1925 to 1974, only three cases of pneumonic plague were reported, all of them thought to be (perhaps with one exception) of the secondary form. From 1975 to 1996, there were 41 human cases of pneumonic plague in the United States, mostly secondary. Of these cases, seven were primary pneumonic plague, of which five clearly resulted from exposure to infected cats and the other two were possibly related to cat exposures. The mode of trans-

mission is as follows: cats living in an area with a reservoir of wild rodent plague hunt the infected rodents, develop a plague infection of the mouth, throat, or lungs, and spread the disease to their owners and to veterinarians.

Although pneumonic plague has the potential for rapid spread, in the United States it has not been very contagious. From 1975 to 1996, there were more than 1,500 human contacts with pneumonic plague cases in the United States without a single incident of person-to-person transmission. Many of the cases were undiagnosed for days after onset of illness, and some were not diagnosed until after death.

Diagnosis of Plague

Laboratory diagnosis of plague is best confirmed by isolating the organism from blood or other clinical materials, although serological testing can detect antibodies to the bacterium in the patient's blood fairly early in the disease. Diagnostic techniques include routine and fluorescent stained smears of blood, bubo aspirate, or sputum; culturing the bacteria from these materials; and indirect identification of the infection using immunological or genetic techniques.[2]

Case definition is as follows. A "suspect" case involves illness with the clinical signs and symptoms of plague, supported by the finding of bacteria with the typical morphology and staining properties of *Yersinia pestis*. A "presumptive" case is an illness having the clinical signs and symptoms of plague and a positive fluorescent-antibody test or a single positive serology—that is, the presence of a specific antibody to the bacterium in the patient's blood serum. A "confirmed" case is one in which *Yersinia pestis* has been isolated from the patient and cultured in growth medium, and the identity of the bacteria has been confirmed (e.g., through bacteriophage lysis). Culturing plague can be difficult: during the first 24 or 36 hours of incubation, the bacterial colonies are tiny—less than 2 millimeters in diameter—and can be easily overgrown or otherwise missed. Another means of confirming the diagnosis is to detect a four-fold rise in the patient's antibody titer to *Yersinia pestis* between serum specimens taken during the acute and convalescent phases of the illness.

Treatment of Plague

Standard treatment for plague is with aminoglycoside antibiotics. Streptomycin is the drug of choice, although gentamycin is probably as efficacious. Tetracyclines are also highly effective. Chloramphenicol is particularly useful for treating plague infections of the membranous coverings of the lungs and brain because it penetrates well into tissues and tissue spaces. For prophylaxis, tetracycline, doxycycline, and trimethoprim sulfamethoxazole have all been used with apparent success.

Prevention of Plague

The best way for persons to reduce their risk of acquiring plague is to avoid areas where the disease infects an animal reservoir, as indicated by the unusual death of rats and other rodents. When susceptible animals are infected with *Yersinia pestis* and die, their fleas seek alternative hosts, including humans. Other means of preventing plague include improved environmental sanitation and the use of personal protection against fleas. Antibiotic prophylaxis can provide effective protection for short periods of high-intensity exposure, such as when working in an area where a plague outbreak has occurred in humans or animals. Doxycycline is a good means of prophylaxis in adults for a two- or three-week period.

The plague vaccine available in the United States is a killed vaccine that requires several doses over a period of months to generate effective immunity. This vaccine appears to protect against contract-

ing bubonic plague and may modify pneumonic plague, but it does not provide full protection against respiratory spread. Russia and a few other countries have developed live, weakened plague vaccines, which have not been shown to be more effective than killed vaccines and cause unpleasant side effects such as localized pain, fever, and other systemic symptoms.

Vaccination of U.S. troops against plague has not been intended to defend against deliberate use of plague as a warfare agent, but rather to protect against natural exposure to the bubonic form of the disease. During the Vietnam War, all American troops sent to the theater were immunized against plague and few cases were reported, despite a high incidence of endemic typhus (also transmitted by the oriental rat flea). Since bubonic plague was common in the Vietnamese population at the time, the vaccine appears to have given U.S. troops adequate protection. Although one or two cases of pneumonic plague did occur, the disease was milder than expected. Thus, while the vaccine did not fully protect against pneumonic plague, it may have moderated its effects.

Control of Plague

The first line of defense against plague outbreaks is an epidemiological surveillance system capable of identifying the infection in animals and their fleas and of detecting and confirming human cases early on. Diagnosis must be followed by the prompt isolation and treatment of early cases and the identification of contacts, followed by antibiotic prophylaxis or surveillance. Insecticides can be used to control fleas in the environment and should be applied before exterminating the rodent hosts. If the rodents are killed prior to the flea-control campaign, the fleas will migrate from the dead rodents to other hosts, including humans.

Antibiotic-Resistant Strains of Plague

Some strains of *Yersinia pestis* have been identified that are fully or partially resistant to one, two, or three standard antibiotics, such as tetracycline and streptomycin. The first confirmed multidrug-resistant strain was recently isolated and characterized from a bubonic plague patient in Madagascar.[3] This infection was resistant to all antibiotics used to treat plague with the exception of trimethoprim sulfamethoxazole, to which the patient fortunately responded. Antibiotic resistance in *Yersinia pestis* appears to be mediated by a plasmid (a closed loop of non-chromosomal DNA) that is also present in other bacteria, since scientists were able to observe the exchange of the plasmid between *Yersinia pestis* and the common intestinal bacterium *Escherichia coli* in the laboratory. Nevertheless, the multiple drug-resistance pattern seen in the Madagascar patient has not since been detected in other patients, in rats or fleas collected in the same area, or in plague strains examined retrospectively or collected anywhere else in the world.

Conclusions

Yersinia pestis is a virulent microorganism that can cause outbreaks of acute, incapacitating illness with a high fatality rate. Plague's pandemic history, and the potential for severe complications in individual cases, continue to elicit public dread. Pneumonic plague, the most deadly form of the disease, can be transmitted from person to person by respiratory droplet infection. Outbreaks of pneumonic plague are infrequent and can be controlled by early detection of cases and contacts, isolation and treatment of cases, and by prophylactic administration of antibiotics to close contacts. Bubonic plague can be controlled by eliminating vector fleas in the environment with

the use of insecticides and by exterminating the rodent hosts. Plague vaccine has limited use for protecting laboratory workers and others who handle the plague bacillus routinely and persons exposed to infected rodents and their fleas. The disease is curable with antibiotics, but treatment must be specific and initiated early in the illness to prevent fatalities.

References

1. These different strains, or "biotypes," can be identified by their ability to ferment glycerol and reduce nitrate or by profiling their ribosomal RNA.
2. Indirect diagnostic techniques for plague include hemagglutination testing or enzyme immunoassay. A bacteriophage virus that specifically infects *Yersinia pestis* serves to confirm its identity in culture. Increasingly, diagnostic laboratories employ the polymerase chain reaction (PCR) to examine tissue specimens for the presence of DNA sequences unique to *Yersinia pestis*.
3. Marc Galimand, Annie Guiyoule, Guy Gerbaud et alia, "Multidrug Resistance in *Yersinia pestis* Mediated by a Transferable Plasmid," *New England Journal of Medicine*, **337**, 10, September 4, 1997, pp. 677–680. See also the editorial in the same issue: David T. Dennis and James M. Hughes, "Multidrug Resistance in Plague," pp. 702–704.

Appendix B: List of Acronyms

BW	biological warfare/weapons
BWC	Biological and Toxin Weapons Convention
BWCO	[future] Biological Weapons Convention Organization
CBW	chemical and biological warfare/weapons
CDC	U.S. Centers for Disease Control and Prevention
CPI	confidential proprietary information
CW	chemical warfare/weapons
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
DOE	U.S. Department of Energy
FAO	UN Food and Agriculture Organization
OIE	Organisation Internationale des Epizootiques/International Organization of Epizootics
PCR	polymerase chain reaction
ProMED	Program on Monitoring Emerging Diseases
R&D	research and development
UK	United Kingdom
UNSCOM	United Nations Special Commission on Iraq
WHO	World Health Organization

Appendix C: Workshop Agenda

Workshop on Procedures for Investigating Suspicious Outbreaks of Infectious Disease in a Noncooperative Environment

Building 170, Room 1091
Lawrence Livermore National Laboratory
Livermore, California
May 12-13, 1998

Agenda

Monday, May 11, 1998

Arrival of Participants at Bay Area Airports

Tuesday, May 12, 1998

7:00 – 8:00 am	Breakfast at hotel
7:45 am	Badging at hotel
8:15 am	Shuttle bus from Hampton Inn Hotel to Lawrence Livermore National Laboratory, Building 70, Rm 1091
8:30 – 8:45 am	Welcome – Ron Lehman, Jonathan Tucker
8:45 – 9:45 am	"Experience with Recent International Field Investigations and Concerns Related to Biological Warfare" – James LeDuc, Centers for Disease Control and Prevention

9:45 – 10:45 am	"The 1979 Sverdlovsk Anthrax Outbreak" – Matthew Meselson, Harvard University, and Jeanne Guillemin, Boston College
10:45 – 11:00 am	Coffee break
11:00 – 11:45 am	"A Primer on Plague" – David Dennis, Centers for Disease Control and Prevention
11:45 – 12:00 n	"Overview of the Workshop Scenario" – Jonathan B. Tucker, Center for Nonproliferation Studies
12:15 – 1:30 pm	Lunch
1:30 – 3:15 pm	Working Group meetings Working Group A: Initiation of a Field Investigation Working Group B: Conduct of a Field Investigation Working Group C: Transition to a Facility Investigation Working Group D: Conduct of a Facility Investigation
3:13 – 3:30 pm	Break
3:30 – 5:30 pm	Working Group meetings
5:45 pm	Reception, Building 125 Dining Facility Dinner, Followed by Keynote Address: "Distinguishing Natural from Artificial Disease Outbreaks," Donald A. Mahley, U.S. Arms Control & Disarmament Agency

Wednesday, May 13, 1998

7:00 – 8:00 am	Breakfast at hotel
8:15 am	Shuttle bus from hotel to LLNL
8:30 – 10:00 am	Working Group meetings (continued)
10:00 – 10:30 am	Coffee break
10:30 – 11:30 am	Report by Working Group A Discussion
11:30 – 12:30 pm	Report by Working Group B Discussion
12:30 – 1:30 pm	Lunch

1:30 – 2:30 pm	Report by Working Group C Discussion
2:30 – 3:30 pm	Report by Working Group D Discussion
3:30 – 4:00 pm	Coffee break
4:00 – 5:30 pm	Wrap-up and discussion of workshop proceedings
5:30 pm	Evening free, departure of some participants

Appendix D: List of Workshop Participants

Ms. Susan Allen
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Dr. Kathleen Bailey
Political Scientist
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